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<p>(54) Title: METHODS AND COMPOUNDS FOR TREATING DEPRESSION AND OTHER DISORDERS</p> <p>(57) Abstract</p> <p>The present invention features compounds active at both the serotonin uptake site and the N-methyl-D-aspartate (NMDA) receptor and the use of such compounds for treating different disorders. Compounds having activity at the serotonin reuptake site and the NMDA receptor ("multi-active compounds") can be used to treat different types of disorders such as depression, obsessive-compulsive disorders (OCD), sleep disorders, sexual dysfunction, and eating disorders. Preferably, the multi-active compounds are used to treat depression.</p>			

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METHODS AND COMPOUNDS FOR TREATING DEPRESSION
AND OTHER DISORDERS

RELATED APPLICATIONS

5 This application claims priority to provisional application serial number 60/092,546.

FIELD OF THE INVENTION

This invention relates to the use of compounds and 10 pharmaceutical compositions for the treatment of depression and other disorders. More specifically, this invention relates to compounds that are active at monoamine reuptake sites, such as the serotonin reuptake site, and the NMDA receptor.

15 BACKGROUND OF THE INVENTION

The following description provides a summary of information relevant to the present invention. It is not an admission that any of the information provided herein is prior art to the presently claimed invention, nor that any of the publications 20 specifically or implicitly referenced are prior art to the present invention.

Depression is a common illness associated with substantial morbidity and mortality. Major depression is characterized by feelings of despair, intense sadness, mental slowing, loss of 25 concentration, pessimistic worry, agitation, and self-deprecation. Physical changes which can accompany depression, particularly in severe or "melancholic" depression, include insomnia or hypersomnia; anorexia and weight loss (or occasionally overeating); less energy and libido; and disruption 30 of normal circadian rhythms of activity, body temperature, and different endocrine functions. (Baldessarini, in Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 9th Ed. Chapt. 19, McGraw-Hill, 1996.)

It is well known that compounds which block the reuptake of 35 monoamines such as serotonin (serotonin-selective reuptake site

inhibitors or SSRIs) possess antidepressant activity (U.S. Pat. Nos. 4,314,081, and U.S. Pat. No. 4,626,549, Molley and Schmiegel). Also, several lines of evidence suggest that NMDA receptor antagonists which demonstrate functional antidepressant 5 activity in several animal models (Skolnick, P., Editor, "Antidepressant: New Pharmacological Strategies", National Institutes of Health, Bethesda MD, 1998), may provide a useful approach to treating depression.

However, prior to the present invention, it was not 10 recognized that compounds which are active at both monoamine reuptake sites, including the serotonin reuptake site, and the N-methyl-D-aspartate (NMDA) receptor and the use of such multi-active compounds would be beneficial for treating depression and other disorders.

15

SUMMARY OF THE INVENTION

The present invention features compounds active at both the serotonin reuptake site and the N-methyl-D-aspartate (NMDA) receptor and the use of such compounds for treating different 20 disorders. Compounds having activity at the serotonin reuptake site and the NMDA receptor ("multi-active compounds") can be used to treat different types of disorders such as depression, obsessive-compulsive disorders (OCD), sleep disorders, sexual dysfunction, and eating disorders. Preferably, the multi-active 25 compounds are used to treat depression.

The ability of the multi-active compounds to act effectively at both the serotonin reuptake site and NMDA receptor enhances, rather than detracts, from their effectiveness. In general, potent activity at the serotonin reuptake site is 30 favored, while an intermediate activity at the NMDA receptor is favored. Too potent an activity at the NMDA receptor is less preferred because of possible PCP-like side effects. Activity at the serotonin reuptake site and the NMDA receptor can be measured using techniques well known in the art.

Examples of assays which can be employed to measure serotonin reuptake site and NMDA receptor activities include the "serotonin reuptake inhibition assay," or "SSRI assay," the "NMDA assay," and the [³H]MK-801 binding assay which are described in
5 Example 1. Preferred compounds have an IC₅₀ at the serotonin reuptake site less than or equal to about 100 nM, less than or equal to about 10 nM, or less than or equal to about 1 nM as measured by the serotonin reuptake inhibition assay.

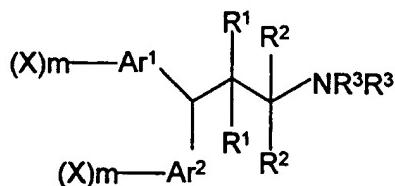
Preferred compounds also have an IC₅₀ at the NMDA receptor
10 of between about 50 nM to about 1 μ M as measured by the NMDA assay. More preferably, the IC₅₀ at the NMDA receptor is about 100 nM to about 800 nM; and even more preferably about 500 nM.

Thus, a first aspect of the present invention features a method of treating a patient for depression comprising the step
15 of administering an effective amount of a compound having an NMDA IC₅₀ of about 50 nM to about 1 μ M as measured in the NMDA assay and a serotonin reuptake IC₅₀ of less than or equal to about 100 nm as measured in the serotonin reuptake inhibition assay.

Another aspect of the present invention features a method
20 of treating a patient for depression comprising the step of administering to the patient an effective amount of a compound having the chemical structure:

Structure I

25



wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃,
30 -O-alkyl, and -O-acyl;

Ar¹ and Ar² are each independently selected from the group consisting of phenyl, naphthyl, thiofuranyl, tetrahydronaphthyl, furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl, 5 cycloheptyl, and cyclopentyl (as indicated in Structure I, Ar¹ and Ar² may be substituted);

each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;

each R² is independently selected from the group consisting 10 of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino;

each R³ is independently selected from the group consisting of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; and

each m is independently an integer from 0 to 5;

provided that if both R³'s are -CH₃, then both X_m's are not 15 3-F, 4-F, 3-CF₃, 4-Cl, and if both R₃'s are -CH₃ and one X_m is 4-F, then the other X_m is not 4-Cl; further provided that if one R₃ is -H and the other R₃ is -CH₃, then both X_m's are not 4-Cl, and if one R₃ is -H and the other R₃ is -CH₃ then at least one m is 1, or a pharmaceutically acceptable salt thereof.

By "alkyl" is meant a branched chain, straight chain, or cyclic, hydrocarbon containing between 1 and 6 carbon atoms, preferably between 1 and 4 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, 2-methylpentyl, cyclopropylmethyl, and 25 cyclobutylmethyl. Preferably, the alkyl is a branched or straight chain.

By "hydroxyalkyl" is meant an alkyl group as defined above, substituted with a hydroxyl group.

By "alkylphenyl" is meant an alkyl group as defined above, 30 substituted with a phenyl group.

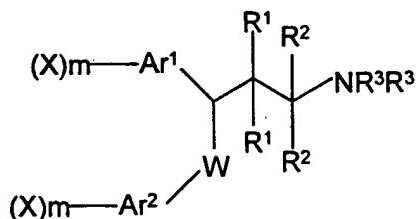
By "acyl" is meant -C(O)R, where R is H or alkyl as defined above, such as, e.g., formyl, acetyl, propionyl, or butyryl; or, R is -O-alkyl such as in alkyl carbonates or R is N-alkyl such as in alkyl carbamates.

Another aspect of the present invention features a method of treating a patient for depression comprising the step of administering to the patient an effective amount of a compound having the chemical structure:

5

Structure II

10

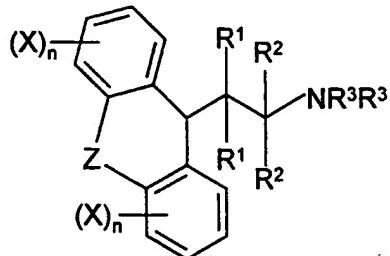


wherein Ar¹, Ar², each R¹, each R², each R³, each X, and m is as described above for Structure I compounds, and W is either -CH₂-, -O-, or -S-.

15 Another aspect of the present invention features a method of treating a patient for depression comprising the step of administering to the patient an effective amount of a compound having the chemical structure:

20

Structure III



wherein each R¹, each R², each R³, and each X is as described above for Structure I compounds, each n is

independently 1 to 4, and Z is either -CH₂CH₂- , -CH₂CH(CH₃)-, -CH=CH-, -O-CH₂- , -S-CH₂- , -CH₂- , -O-, or -S-.

Other aspects of the present invention describes multi-active compounds and pharmaceutical compositions containing such 5 compounds. Examples of multi-active compounds covered by this aspect of the present invention are those novel compounds included in Table I (Example 1), and the pharmaceutically acceptable salts thereof.

Various examples are described herein. These examples are 10 not intended in any way to limit the claimed invention.

Other features and advantages of the invention will be apparent from the following drawing, the description of the invention, the examples, and the claims.

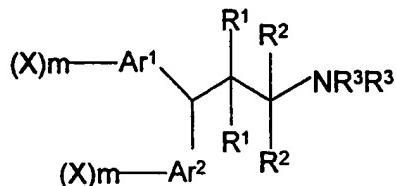
15 DETAILED DESCRIPTION OF THE INVENTION

The present invention features compounds active at both the serotonin reuptake site and the NMDA receptor and the use of such compounds for treating different disorders. As illustrated in the examples provided below, such compounds may also have 20 significant activity at other sites such as the dopamine reuptake site and the norepinephrine reuptake site.

The methods and compounds described herein are particularly useful for treating patients having different types of disorders such as depression, compulsive obsessive disorders, sleep 25 disorders, sexual dysfunction, and eating disorders. Preferably, the methods and compounds are used to treat depression.

Structure I Compounds

Structure I compounds are as follows:



wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, and -O-acyl; ; preferably, each X is independently either -F, -Cl, -OCF₃ or -CF₃;

5 Ar¹ and Ar² are each independently selected from the group consisting of phenyl, naphthyl, thiofuranyl, tetrahydronaphthyl, furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl, cycloheptyl, and cyclopentyl; preferably Ar¹ and Ar² are
10 independently naphthyl or phenyl; more preferably at least one of Ar¹ and Ar² is phenyl; and more preferably, both Ar¹ and Ar² are phenyl;

each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;
15 preferably, each R¹ is -H;

each R² is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino; preferably each R² is -H;

20 each R³ is independently selected from the group consisting of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; preferably, each R³ is independently either -H or -CH₃; more preferably one R³ is -H, and the other R³ is either -H or -CH₃; and

each m is independently an integer from 0 to 5; and preferably, each m is independently 0 or 1;

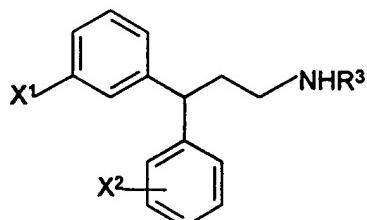
25 provided that if both R³'s are -CH₃, then both X_m's are not 3-F, 4-F, 3-CF₃, 4-Cl, and if both R₃'s are -CH₃ and one X_m is 4-F then the other X_m is not 4-Cl; further provided that if one R₃ is -H and the other R³ is -CH₃, then both X_m's are not 4-Cl, and if one R³ is -H and the other R³ is -CH₃, then at least one m is 1;

30 or a pharmaceutically acceptable salt thereof.

Substitutions in both the Structure I upper and lower phenyl rings are useful for providing serotonin reuptake site and NMDA receptor activities. The effect of different substitution patterns is illustrated in the data provided in Example 1.

An embodiment is provided by Structure IV compounds as follows:

Structure IV

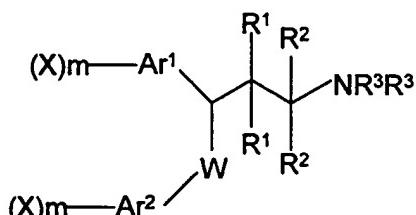


5

- wherein X¹ is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH,
-OCF₃, -O-alkyl, or -O-acyl; preferably, X¹ is either -F, -Cl,
-OCF₃ or -CF₃; and more preferably X¹ is -F;
- 10 X² is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃,
-O-alkyl, or -O-acyl; preferably, X² is independently either -F,
-Cl, -OCH₃, -CH₃, -OCF₃ or -CF₃; more preferably, X² is either 2-
OCH₃, 2-CH₃, 3-F, 3-CF₃, or 4-CF₃; and
R³ is either -H or CH₃;
- 15 or a pharmaceutically acceptable salt thereof.

Structure II

Structure II compounds have the following structure:



20

- wherein Ar¹, Ar², each R¹, each R², each R³, each X, and m is as described above for Structure I compounds, including preferred substituents; preferably 1; and W is either -CH₂-, -O-, or -S-.

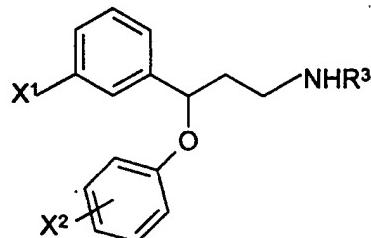
- 25 Substitution in both the Structure II upper and lower phenyl rings are useful for providing serotonin reuptake site and

NMDA receptor activities. In general, substitutions in the structure I upper phenyl ring are particularly useful for enhancing NMDA receptor activity, while substitutions in the lower phenyl ring are particularly useful for enhancing serotonin 5 reuptake site activity.

An embodiment is provided by Structure V compounds as follows:

10

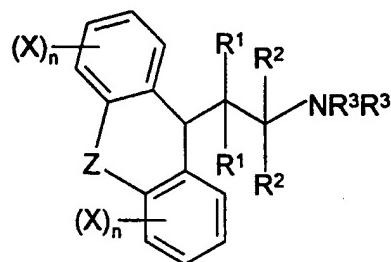
Structure V



wherein X¹, X², and R³ are as described above for Structure IV compounds, including the preferred embodiments; or a pharmaceutically acceptable salt thereof.

Structure III

Structure III compounds having the following chemical structure:



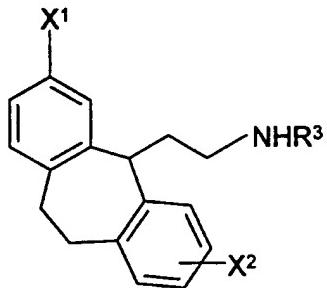
10

- wherein each R¹, each R², each R³, and each X, is as described above for Structure I compounds, including preferred embodiments; n is 1 to 4, preferably 1; and Z is either -CH₂CH₂-, -CH₂CH(CH₃)-, -CH=CH-,
- 5 -O-CH₂-, -S-CH₂-, -CH₂-, -O-, or -S-, preferably, Z is -CH₂CH₂-; or a pharmaceutically acceptable salt thereof.

An embodiment is described by Structure VI compounds as follows:

10

Structure VI

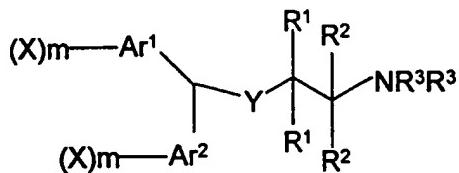


15 wherein X¹ is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl; preferably, X¹ is either -F, -Cl, -OCF₃, or -CF₃; and more preferably X¹ is -F;

20 X² is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl; preferably, X² is either -F, -Cl, -OCH₃, -CH₃, -OCF₃, or -CF₃; and

R³ is either hydrogen or methyl; or a pharmaceutically acceptable salt thereof.

Structure VII compounds have the following chemical structure:



wherein each X is independently selected from the group
 5 consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃,
 -O-alkyl, and -O-acyl; ; preferably, each X is independently
 either -F, -Cl, -OCF₃ or -CF₃;

Ar¹ and Ar² are each independently selected from the group
 consisting of phenyl, naphthyl, thifuranyl, tetrahydronaphthyl,
 10 furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl,
 tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl,
 cycloheptyl, and cyclopentyl; preferably Ar¹ and Ar² are
 independently naphthyl or phenyl; more preferably at least one of
 Ar¹ and Ar² is phenyl; and more preferably, both Ar¹ and Ar² are
 15 phenyl;

Y is either -CH₂- , -O-, or -S-;

each R¹ is independently selected from the group consisting
 of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;
 preferably, each R¹ is -H;

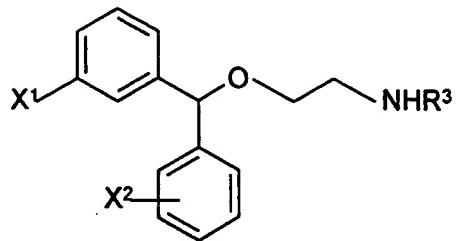
20 each R² is independently selected from the group consisting
 of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino;
 preferably each R² is -H;

each R³ is independently selected from the group consisting
 of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; preferably, each
 25 R³ is independently either -H or -CH₃; more preferably one R³ is
 -H, and the other R³ is either -H or -CH₃; and

each m is independently an integer from 0 to 5; and
 preferably, each m is independently 0 or 1.

30 An embodiment is provided by Structure VIII compounds as
 follows:

Structure VIII



wherein X^1 is independently selected from the group consisting of -H, -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl; preferably, X^1 is either -F, -Cl, -OCF₃, and -CF₃;

5 X^2 is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃; and more preferably X^1 is para -CF₃;

-O-alkyl, or -O-acyl; preferably, X^2 is independently either -F, -Cl, -OCH₃, -CH₃, -OCF₃ or -CF₃; more preferably, X^2 is either 2-OCH₃, 2-CH₃, 3-F, 3-CF₃, or 4-CF₃; and

10 R³ is either -H or CH₃;

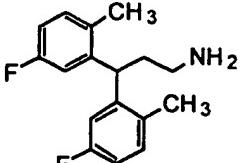
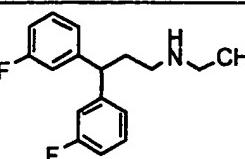
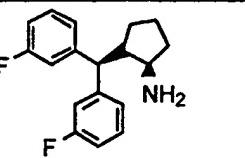
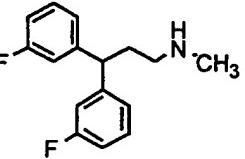
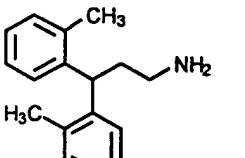
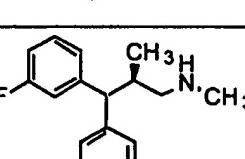
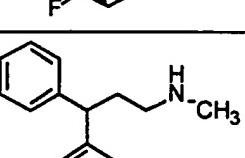
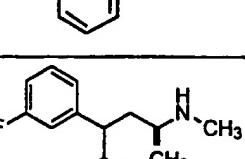
or a pharmaceutically acceptable salt thereof.

Certain compounds of the present invention are presented
15 below in Tables I. Examples of certain antidepressant compounds are shown in Table II.

Table I

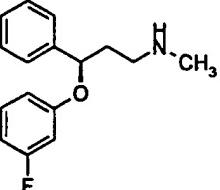
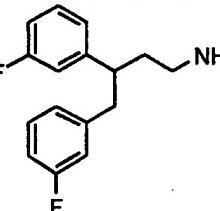
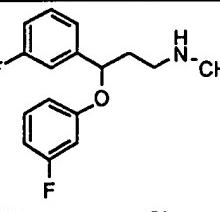
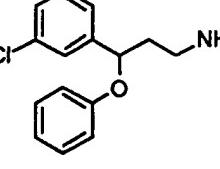
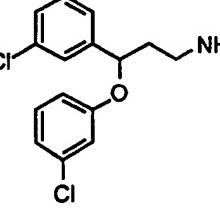
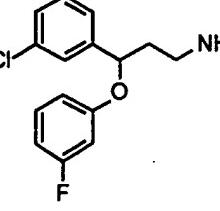
Comp.	Structure	fura2 data IC ₅₀ (μM)	[³ H]MK-801 data IC ₅₀ (μM)	5-HT Uptake	NE Uptake	DA Uptake
19		0.435	2.1 89.2	18.2 52.6	2.8	6.7 75.0
20		0.070	0.252	K _i = 0.256	K _i = 0.312	K _i = 3.0

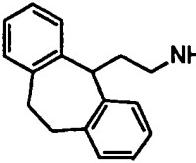
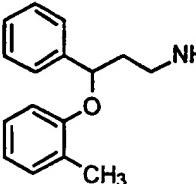
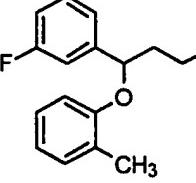
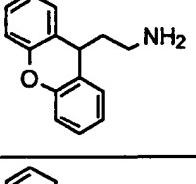
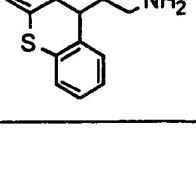
33		0.060	0.181	K _i = 1.2	K _i = 3.8	K _i = 0.826
34		0.426	2.7	K _i = 2.1	K _i = 3.0	K _i = 0.602
50		0.089	0.762	K _i = 0.045	K _i = 0.107	K _i = 1.8
46		0.013	5.2	10.4 75.4	7.4 64.0	40.2 97.1
236						
237						
63		0.093	0.245	13.4 84.6	6.8 76.2	64.3 97.8

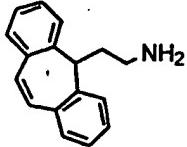
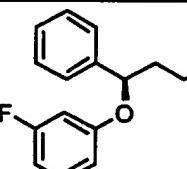
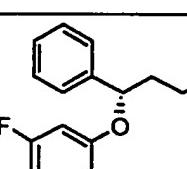
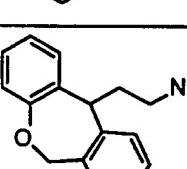
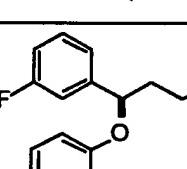
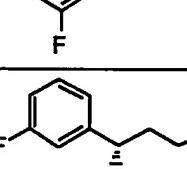
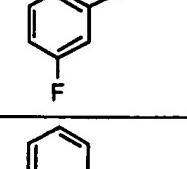
58		0.028	0.203	27.2 95.2	1.3 66.6	0.0 45.2
59		0.272	0.453	14.3 85.7	7.4 50.6	1.6 77.6
64		0.309	0.851	K _i = 0.252	K _i = 0.508	K _i = 0.119
60		0.416	0.641	K _i = 0.068	K _i > 10.0	K _i = 0.914
65		0.167	2.0	K _i = 0.127	K _i = 0.306	K _i = 22.0
66		0.236	1.2	6.1 67.5	4.2 36.5	4.4 92.8
67		10.95	2.9			
69		0.224	0.366			

108		1.06	0.942			
111		0.645	0.167	K _i = 0.600	K _i = 0.124	K _i = 0.030
216						
217						
118		0.409	0.240	K _i = 0.131	K _i = 0.262	K _i = 4.1
N-methyl- 118						
N-methyl- 118						

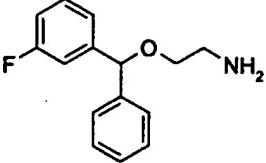
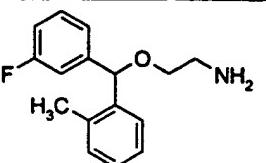
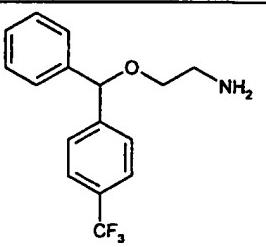
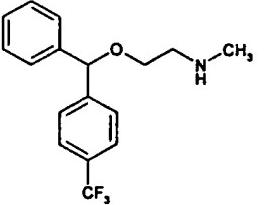
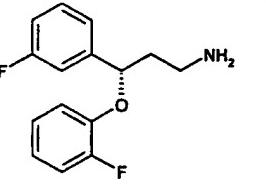
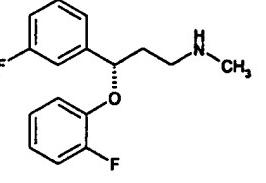
119		0.115	0.087	0.6 3.1	8.9 19.4	1.9 58.3
120		0.101	0.074			
121		0.656	0.670	8.5 84.3	33.6 94.9	1.8 91.3
122		0.209	0.342	K _i = 0.062	K _i = 0.103	K _i = 2.8
137		0.232	0.074			
221						

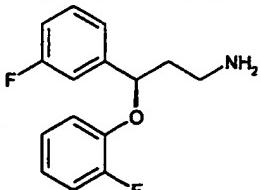
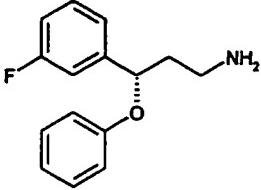
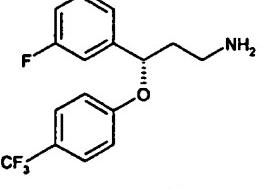
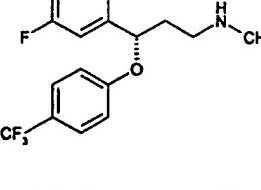
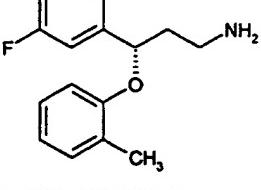
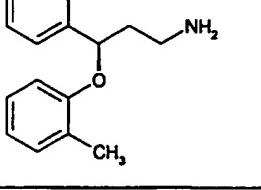
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142		1.013	1.54			
144						
145		0.098	0.626	3.5 81.1	16.6 99.4	0.0 87.4
148		0.549	0.373			
149		0.085	0.150			
150		0.195	0.351			

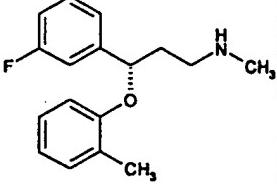
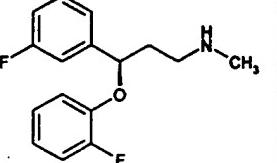
156		0.069	0.090	$K_1 = 1.2$	$K_1 = 0.570$	$K_1 > 10.0$
177			0.754	$K_1 = 0.056$	$K_1 = 0.109$	$K_1 > 10.0$
178			1.25			
179			1.67			
181		0.081	0.632	37.4 74.2	10.7 32.0	0.0 108.8
182		2.6	7.05			
183		0.676	5.01			

184		1.5	1.51			
185		0.646	0.639	$K_i = 2.4$	$K_i = 0.858$	$K_i = 1.1$
186		0.155	0.123	$K_i = 0.022$	$K_i = 0.136$	$K_i = 3.1$
187		1.78	2.01			
191			1.3	$K_i = 0.134$	$K_i = 0.638$	$K_i = 1.55$
192			0.111	$K_i = 0.014$	$K_i = 0.325$	$K_i = 1.3$
193			>1.0			

194			0.371			
195			0.029			
196			2.24			
197			0.053	9.8 58.1	0.0 27.5	0.0 83.5
198						
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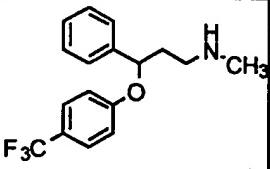
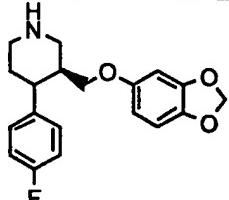
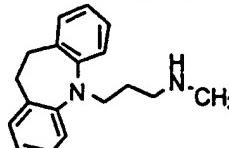
228						
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top numbers for 5-HT (serotonin assay), NE (norepinephrine assay), and DA (dopamine assay) refer to mean % inhibition (\pm SEM) @ 100 nM, (except where K_i values (μ M) are indicated)

bottom numbers for 5HT, NE, and DA refer to mean % inhibition (5 (\pm SEM) @ 10.0 μ M, (except where K_i [μ M] values are indicated).

Table II

Comp.	Structure	fura2 data IC50 (μ M)	[3 H]MK-801 data	5-HT Uptake	NE Uptake	DA Uptake
Fluoxetine		3.4	No activity at 10 μ M	> 60 % 99 %	0 68	0 78
Paroxetine				> 80 % 98 %	<20 50	<20 97
Desipramine		2.3		<20 90	<20 72	<20 64

Bupropion				n.t. <20	n.t. <20	<20 99
Phenylphenoxy-propylamine		0.829	0.372			
Nisoxetine		1.23		+		
Flunamine						

top numbers for 5-HT (serotonin assay), NE (norepinephrine assay), and DA (dopamine assay) refer to mean % inhibition (\pm SEM) @ 100 nM.

5 bottom numbers for 5HT, NE, and DA refer to mean % inhibition (\pm SEM) @ 10.0 μ M.
n.t. indicates not tested.

Administration

10 The methods and compounds will typically be used in therapy for human patients. However, they may also be used to treat similar or identical diseases in other vertebrates such as other primates, sports animals, and pets such as horses, dogs and cats.

15 Suitable dosage forms, in part, depend upon the use or the route of administration, for example, oral, transdermal, transmucosal, or by injection (parenteral). Such dosage forms should allow the compound to reach target cells. Other factors are well known in the art, and include considerations such as toxicity and
20 dosage forms that retard the compound or composition from

exerting its effects. Techniques and formulations generally may be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Co., Easton, PA, 1990 (hereby incorporated by reference herein).

- 5 Compounds can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts are non-toxic salts in the amounts and concentrations at which they are administered. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of a compound
10 without preventing it from exerting its physiological effect. Useful alterations in physical properties include lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.
- 15 Pharmaceutically acceptable salts include acid addition salts such as those containing sulfate, chloride, hydrochloride, fumarate, maleate, phosphate, sulfamate, acetate, citrate, lactate, tartrate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, cyclohexylsulfamate and
20 quinate. Pharmaceutically acceptable salts can be obtained from acids such as hydrochloric acid, maleic acid, sulfuric acid, phosphoric acid, sulfamic acid, acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic
25 acid, cyclohexylsulfamic acid, fumaric acid, and quinic acid.

Pharmaceutically acceptable salts also include basic addition salts such as those containing benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, calcium, lithium, magnesium,
30 potassium, sodium, ammonium, alkylamine, and zinc, when acidic functional groups, such as carboxylic acid or phenol are present. For example, see Remington's Pharmaceutical Sciences, 19th ed., Mack Publishing Co., Easton, PA, Vol. 2, p. 1457, 1995. Such salts can be prepared using the appropriate corresponding bases.

Pharmaceutically acceptable salts can be prepared by standard techniques. For example, the free-base form of a compound is dissolved in a suitable solvent, such as an aqueous or aqueous-alcohol in solution containing the appropriate acid 5 and then isolated by evaporating the solution. In another example, a salt is prepared by reacting the free base and acid in an organic solvent.

The pharmaceutically acceptable salt of the different compounds may be present as a complex. Examples of complexes 10 include 8-chlorotheophylline complex (analogous to, e.g., dimenhydrinate: diphenhydramine 8-chlorotheophylline (1:1) complex; Dramamine) and various cyclodextrin inclusion complexes.

Carriers or excipients can be used to produce pharmaceutical compositions. The carriers or excipients can be 15 chosen to facilitate administration of the compound. Examples of carriers include calcium carbonate, calcium phosphate, various sugars such as lactose, glucose, or sucrose, or types of starch, cellulose derivatives, gelatin, vegetable oils, polyethylene glycols and physiologically compatible solvents. Examples of 20 physiologically compatible solvents include sterile solutions of water for injection (WFI), saline solution, and dextrose.

The compounds can be administered by different routes including intravenous, intraperitoneal, subcutaneous, intramuscular, oral, transmucosal, rectal, or transdermal. Oral 25 administration is preferred. For oral administration, for example, the compounds can be formulated into conventional oral dosage forms such as capsules, tablets, and liquid preparations such as syrups, elixirs, and concentrated drops.

Pharmaceutical preparations for oral use can be obtained, 30 for example, by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, 35 including lactose, sucrose, mannitol, or sorbitol; cellulose

preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose (CMC), and/or polyvinylpyrrolidone (PVP: povidone). If desired,
5 disintegrating agents may be added, such as the cross-linked polyvinylpyrrolidone, agar, or alginic acid, or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may
10 optionally contain, for example, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol (PEG), and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dye-stuffs or pigments may be added to the tablets or dragee coatings for identification or to
15 characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin ("gelcaps"), as well as soft, sealed capsules made of gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the
20 active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid
25 polyethylene glycols (PEGs). In addition, stabilizers may be added.

Alternatively, injection (parenteral administration) may be used, e.g., intramuscular, intravenous, intraperitoneal, and/or subcutaneous. For injection, the compounds of the
30 invention are formulated in sterile liquid solutions, preferably in physiologically compatible buffers or solutions, such as saline solution, Hank's solution, or Ringer's solution. In addition, the compounds may be formulated in solid form and redissolved or suspended immediately prior to use. Lyophilized
35 forms can also be produced.

Administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, 5 and include, for example, for transmucosal administration, bile salts and fusidic acid derivatives. In addition, detergents may be used to facilitate permeation. Transmucosal administration, for example, may be through nasal sprays or suppositories (rectal or vaginal).

10 The amounts of various compound to be administered can be determined by standard procedures taking into account factors such as the compound IC₅₀, the biological half-life of the compound, the age, size, and weight of the patient, and the disorder associated with the patient. The importance of these 15 and other factors are well known to those of ordinary skill in the art. Generally, a dose will be between about 0.01 and 50 mg/kg, preferably 0.1 and 20 mg/kg of the patient being treated. Multiple doses may be used.

20 Additional examples are provided below illustrating different aspects and embodiments of the present invention. These examples are not intended in any way to limit the disclosed invention.

25 Example 1: Pharmacological Effects of Different Compounds

This example illustrates the activity of different compounds at different monoamine reuptake sites and the NMDA receptor. Table I illustrates the activities at different monoamine reuptake sites and the NMDA receptor, and compounds 30 expected to have significant activity at the serotonin reuptake site and the NMDA receptor. Table II provides the activities of different anti-depressants at different monoamine reuptake sites and the NMDA receptor.

35 MONOAMINE TRANSPORTER BINDING ASSAYS

Monoamine transporter binding assays (reuptake inhibition assays) were performed by NovaScreen using standard radioligand binding assays. The transporter binding assays are described briefly below:

5

Serotonin Reuptake Inhibition Assay

Rat forebrain membranes were incubated with 0.7 nM [³H]citalopram, N-methyl, (70-87 Ci/mmol) in 50 mM Tris-HCl (pH 7.4), 120 mM NaCl, and 5 mM KCl at 25 °C for 60 minutes.

10 Nonspecific binding was determined using 10 µM clomipramine and imipramine was used as the positive control reference compound. Reactions were terminated by rapid vacuum filtration onto glass fiber filters. Bound radioactivity was determined using liquid scintillation spectrometry and experimental values were compared 15 to control values to determine binding to the serotonin transporter site (based on D'Amato, R.J. et al., *J. Pharmacol. Exp. Ther.*, 242, 364-371, 1987, and Brown, N.L. et al., *Eur. J. Pharmacol.*, 123, 161-165, 1986).

20 Norepinephrine Reuptake Inhibition Assay

Rat forebrain membranes were incubated with 1.0 nM [³H]nisoxetine (60-85 Ci/mmol) in 50 mM Tris-HCl (pH 7.4), 300 mM NaCl, and 5 mM KCl at 0-4 °C for 4 hours. Nonspecific binding was determined using 1.0 µM desipramine and desipramine was used 25 as the positive control reference compound. Reactions were terminated by rapid vacuum filtration onto glass fiber filters. Bound radioactivity was determined using liquid scintillation spectrometry and experimental values were compared to control values to determine binding to the norepinephrine transporter 30 site (Raisman, R. et al., *Eur. J. Pharmacol.*, 78, 345-351, 1982, and Langer, S.Z. et al., *Eur. J. Pharmacol.*, 72, 423-424, 1981).

Dopamine Reuptake Inhibition Assay:

Guinea pig striatal membranes were incubated with 2.0 nM 35 [³H]WIN 35428 (60-87 Ci/mmol) in 50 mM Tris-HC (pH 7.4), 120 mM

NaCl at 0-4 °C for 2 hours. Nonspecific binding was determined using 1.0 µM GBR-12909 and GBR-12909 was used as the positive control reference compound. Reactions were terminated by rapid vacuum filtration onto glass fiber filters. Bound radioactivity 5 was determined using liquid scintillation spectrometry and experimental values were compared to control values to determine binding to the dopamine transporter site (based on Madras, et al., *Molec. Pharmacol.*, 36, 518-524, 1989, and Javitch, J.J., et al., *Molec. Pharmacol.*, 26, 35-44 1984).

10

NMDA RECEPTOR ASSAY

Reagents

All culture media, antibiotics, and enzymes, with the exception of fetal calf serum (Hyclone Laboratories, Logan, UT), 15 were purchased from Sigma Chemical Co., St. Louis, MO. Fura-2/AM was obtained from Molecular Probes, Eugene, OR, and was prepared freshly in dimethylsulfoxide (DMSO) before use. Ionomycin (Calbiochem) was stored as a stock solution in DMSO. Nifedipine (Sigma) and nimodipine (RBI) were dissolved in absolute ethanol. 20 The final concentration of ethanol in the cuvette never exceeded 0.05% and was without effect on basal cytosolic calcium ($[Ca^{2+}]_i$). All other agents were dissolved in phosphate-buffered saline (PBS), and adjusted to pH 7.4

25 Preparation of Rat Cerebellar Granule Cell (RCGC) Cultures

A simple and rapid method for measuring $[Ca^{2+}]_i$ in large homogeneous populations of normal central nervous system neurons has been described in detail (Parks et al., Modulation of N-methyl-D-aspartate receptor-mediated increases in cytosolic 30 calcium in cultured rat cerebellar granule cells. *Brain Res.* 552: 13-22, 1991). Briefly, primary cultures of cerebellar granule neurons were obtained from 8-day-old rats and plated onto squares of Aclar plastic coated with poly-L-lysine. The plastic squares were placed in 12-well culture plates, and ~7.5 x 10⁵ 35 cells were added to each well. Cultures were maintained in

- Eagles's medium containing 25 mM KCl, 10% fetal calf serum, 2 mM glutamine, 100 µg/ml gentamicin, 50 U/ml penicillin, and 50 µg/ml streptomycin at 37 °C in a humid atmosphere of 5% CO₂ in air for 24 hr before the addition of cytosine arabinoside (10 µM, final).
- 5 No changes of culture medium were made until the cells were used for fluorescence recording 6-8 days after plating.

Measurement of Cytosolic Calcium

For measurement of [Ca²⁺]_i, Aclar squares plated with cells 10 were incubated in a HEPES buffer containing 125 mM NaCl, 5 mM KCl, 1.5 mM CaCl₂, 5.6 mM glucose, 25 mM NaHEPES (pH 7.4), 0.1% bovine serum albumin and 2 µM fura-2/acetoxymethyl ester (fura-2/AM) for 30-40 min at 37 °C ("Ca²⁺-free" buffer contained no added CaCl₂ and 30 µM EGTA). The cells were then rinsed with the 15 same buffer, lacking fura-2/AM, and maintained at room temperature until used for measurement of fluorescence, the Aclar squares were transferred into quartz cuvettes containing 2 ml of the HEPES buffer. The cuvette was then placed into a thermostatted holder equipped with a magnetic stirrer in a 20 custom-built spectrofluorimeter (Biomedical Instrumentation Group, University of Pennsylvania, Philadelphia, PA). The size of the plastic Aclar square was such as to fit snugly in the cuvette when placed at a diagonal and therefore suspend itself over the spin bar. Fluorescence was measured using excitation 25 and emission wavelengths of 340 and 510 nm, respectively. The amplitude of the evoked increase in fluorescence and subsequent inhibition were recorded and the concentration of [Ca²⁺]_i was calculated using the formula:

30 $[Ca^{2+}] = K_d (F - F_{min}) / (F_{max} - F)$
 (Eq. 1)

where:

F = fluorescence amplitude evoked at a particular time point or concentration of compound;

F_{\min} = minimum fluorescence determined after the addition of a 2.5 M TRIS/0.3 M EGTA solution;

F_{\max} = maximum fluorescence determined following the addition of 7 mM ionomycin in DMSO; and

5 K_d = dissociation constant for fluorometric indicator (for fura-2, the K_d = 224 nM).

Fluorescent signals were calibrated by adding ionomycin (35-42 μ M, final) to obtain F_{\max} and EGTA (30-12 mM, final, pH 8.2) to obtain F_{\min} .

10

[3 H]MK-801 BINDING ASSAY

Synaptic plasma membranes (SPMs) from rat cortex were prepared as follows. Isolated cerebral cortices from male and female rats were purchased from Pel-Freez (Rogers, AZ) in bulk, 15 and stored at -80 °C. The cortices from 25 rats were thawed and pooled. Tissues were homogenized at 4 °C with a polytron (ESGE Biohomogenizer, #133/1281-0) for 10 pulses at the highest setting in 300 ml of 0.32 M sucrose containing 5 mM K-EDTA (pH 7.0). The resulting homogenates were centrifuged for 10 min at 1,000 \times g 20 in a T865 rotor, UltraPro80 Sorvall Centrifuge. The supernatant was removed and subsequently centrifuged at 30,000 \times g for 30 min. The resulting pellets were resuspended in 250 ml of 5 mM K-EDTA (pH 7.0), stirred on ice for 15 min, and then centrifuged at 30,000 \times g for 30 min. Membranes were washed by re-suspension 25 in 500 ml of 5 mM K-EDTA (pH 7.0), incubated at 32 °C for 30 min with stirring, and centrifuged at 100,000 \times g for 30 min. The final pellet was resuspended in 60 ml of 5 mM K-EDTA (pH 7.0) and stored in aliquots at -80 °C. The extensive washing procedure utilized in this assay was designed to minimize the 30 concentrations of glutamate and glycine (co-agonists at the NMDA receptor-ionophore complex) present in the membrane preparation.

On the day of assay, aliquots of SPM were thawed and resuspended in 75 vols of 5 mM K-EDTA, pH 7.0. SPM were centrifuged at 100,000 \times g for 30 min at 4 °C.

Displacement studies were carried out as follows (Williams et al., Effects of polyamines on the binding of [³H]MK-801 to the NMDA receptor: pharmacological evidence for the existence of a polyamine recognition site. Mol. Pharmacol. 36: 575-581, 5 1989). The SPM pellet was resuspended in assay buffer (30 mM EPPS, 1 mM K-EDTA, pH 7.0) by polytron. MK-801 binding assays were carried out in a incubation volume of 0.5 ml containing 80-100 µg of membrane protein per tube. Duplicate samples were incubated for 2-3 hr at 25°C with < 5 nM [³H]MK-801, 100 µM 10 glycine, 100 µM L-glutamic acid and varying concentrations of displacer. Non-specific binding was determined by the inclusion of 10 µM ketamine or MK-801. Binding was started by the addition of the tissue homogenate. The assay was terminated by the addition of 4 ml ice-cold buffer, followed by filtration over 15 glass-fiber filters (Schleicher & Schuell No. 30) on a Millipore 12-well filtration manifold. Filters were washed with another 3 x 4 ml ice-cold buffer (pH 7.0). Radioactivity on the filters was measured using Fisherbrand Scinti-Safe scintillation cocktail. Samples were shaken for 45-60 min on a shaker platform 20 to solubilize the radioactivity. Counting for ³H was performed in a Beckman 6000IC LS Scintillation Counter for 4 min per sample. Protein was determined as described by Lowry et al. (Protein measurement with the folin phenol reagent. J. Biol. Chem. 193: 265-275, 1951.).

25

Example 2: Antidepressant ActivityCompound 19 Antidepressant Activity

The antidepressant activity of Compound 19 was demonstrated 30 in mice using the tail-suspension test (Steru et al., The Automated Tail Suspension Test: A Computerized Device which Differentiates Psychotropic Drugs, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 11: 659-671, 1987). In this test, the animal is suspended by the tail for 6 minutes. The behavior of the animal 35 is recorded automatically using a special computerized apparatus

which measures two parameters, the duration of immobility and the power of the movements. Ten animals are studied per dose group. Desipramine is used as a reference compound. This test, which is a variant of the behavioral despair test, is based on the 5 assumption that animals faced with an insoluble aversive situation will alternate between phases of activity (searching to escape) and immobility (waiting, "despair").

Compound 19 was dispersed in a 5% acacia gum suspension, and administered intraperitoneally (i.p.) to male NMRI-CERJ mice, 10 30 min prior to testing, at the single dose of 16 mg/kg. This dose of Compound 19 elicited an 84% decrease in the duration of immobility ($p < 0.001$) and a 275% increase in the power of movements ($p < 0.001$). By comparison, the positive control desipramine (32 mg/kg) produced a 63% decrease in the duration of 15 immobility ($p < 0.001$) and a 71% increase in the power of movements ($p > 0.05$).

Compound 60 Antidepressant Activity

The antidepressant activity of Compound 60 was demonstrated 0 in the forced-swim test (FST) in the mouse and the rat (Porsolt et al., Behavioral Despair in Mice: A Primary Screening Test for Antidepressants, *Arch. Int. Pharmacodyn.* 229: 327-336, 1977; Porsolt et al., Behavioral Despair in Rats: A New Model Sensitive to Antidepressant Treatments, *Eur. J. Pharmacol.* 47: 379-391, 2 1978) and in the mouse tail-suspension test (TST).

For the mouse and rat forced-swim tests, male pathogen-free NIH-Swiss mice (Harlan Sprague-Dawley) weighing between 22-25 g, and male pathogen-free Sprague-Dawley rats (Harlan Sprague-Dawley) weighing between 320-350 g were used. Animals were 30 removed from the housing room to the testing area in their own cages and allowed to adapt to the new environment for at least 1 hour before testing. Mice were administered either drug (imipramine, 10 mg/kg i.p.; or Compound 60, various p.o or i.p. doses) or saline. Thirty minutes to 24 hours later, mice were

placed individually in cylinders (diameter: 10 cm; height: 25 cm) filled with 6 cm of water (22-25°C) for 6 minutes. The duration of immobility during the last 4 minutes of the 6 minute test was scored. A mouse was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water. Results were expressed as the duration of immobility (seconds).

The rat forced-swim test was conducted over two days. On treatment Day 1, rats were placed individually in cylinders (diameter: 18 cm; height: 40 cm) filled with water (22-25°C) to a depth of 15 cm for 15 minutes. The duration of immobility during the first 5 minutes was scored. After testing, the rats were dried with paper towels and placed in holding cages. Five minutes after removal from the testing cylinders, animals received either drug (imipramine, 10 mg/kg i.p.; or Compound 60, various p.o. doses) or saline (p.o.). Ten minutes later, the rats were returned to their home cages. On treatment Day 2, the animals received a second dose of drug or saline, and 1 hour later were placed in the testing cylinders as described above. The duration of immobility during the first 5 minute period was recorded. A rat was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water. Results were expressed as a difference score (duration of immobility on Day 1 minus duration of immobility on Day 2).

For the mouse tail-suspension test with Compound 60, male pathogen-free C57BL/6 mice (Harlan Sprague-Dawley) weighing between 22-25 g were used. Animals were removed from the housing room to the testing area in their own cages and allowed to adapt to the new environment for at least 1 hour before testing. Mice were administered either drug (imipramine, 15 mg/kg i.p.; or Compound 60, various p.o. doses) or saline. Thirty minutes to 24 hours later, the mice were suspended on the edge of a shelf 80 cm

above the floor in the testing room by adhesive tape placed approximately 1 cm from the tip of the tail. The duration of immobility was recorded during a test period of 5 minutes. Mice were considered immobile only when they hung passively and 5 completely motionless. Results were expressed as the duration of immobility (sec).

In the mouse forced-swim test, a single dose of Compound 60, 5 mg/kg p.o., produced a time-dependent reduction in the duration of immobility (Table III), with the peak effect 10 occurring 60 minutes post-dosing. When administered orally 60 minutes before testing, Compound 60 produced a dose-dependent reduction in the duration of immobility (Table IV). The magnitude of the antidepressant-like activity produced by Compound 60 was similar to that elicited by imipramine, 10 mg/kg 15 i.p. (Table IV). Similar antidepressant-like activity was observed when Compound 60 was administered by i.p. injection (Table V).

20 **Table III. Compound 60 produced a time-dependent reduction in the duration of immobility in the mouse FST.**

Time (post-dose)	Mean duration of immobility (sec)	SEM	n
0 (saline control)	128.2	7.5	18
0.5	96.1	11.5	8
1	38.8*	6.1	8
2	66.2*	7.9	8
4	66.9*	13.5	8
6	76.8*	9.0	8
24	124.8	15.9	8

Compound 60 administered as a single dose, 5 mg/kg p.o.

* p < 0.05 compared to saline control.

Table IV. Compound 60 produced a dose-dependent reduction in the duration of immobility in the mouse FST.

Dose (mg/kg)	Mean duration of immobility (sec)	SEM	n
0 (saline control)	129.7	13.3	8
0.625	153.3	12.0	8
1.25	72.3*	7.1	8
2.5	64.5*	13.4	8
5	56.6*	7.1	8
10	68.7*	13.7	6
Imipramine	53.4*	18.6	8

Compound 60 administered as a single oral dose 60 minutes prior to testing.

Imipramine administered as a single dose, 10 mg/kg i.p., 30 minutes prior to testing.

* p < 0.05 compared to saline control.

10

Table V. Compound 60 produced a dose-dependent reduction in the duration of immobility in the mouse FST.

Dose (mg/kg)	Mean duration of immobility (sec)	SEM	n
0 (saline control)	137.8	6.6	22
0.625	139.5	12.8	10
1.25	85.6*	11.5	10
2.5	68.5*	7.1	16
5	89.6*	12.0	6

10	106.1	14.4	6
Imipramine	72.5*	8.7	18

Compound 60 administered as a single i.p. dose 30 minutes prior to testing.

Imipramine administered as a single dose, 10 mg/kg i.p., 30 minutes prior to testing.

5 * p < 0.05 compared to saline control.

Compound 60 produced a dose-dependent antidepressant-like effect in the rat forced-swim test when administered orally 1 hour prior to testing (Table VI). The magnitude of this effect
10 was similar to that produced by imipramine, 10 mg/kg i.p. administered 30 minutes prior to testing.

Table VI. Compound 60 produced a dose-dependent antidepressant-like effect in the rat FST.

Dose (mg/kg)	Mean Change in the Duration of Immobility (Day 2 minus Day 1) (sec)	SEM	n
0 (saline control)	47.9	11.2	14
1.25	29.7	11.2	11
2.5	-24.8*	13.6	9
5	-28.8*	8.5	11
Imipramine	-23.3*	15.2	10

15 Compound 60 administered as a single oral dose 60 minutes prior to testing.

Imipramine administered as a single dose, 10 mg/kg i.p., 30 minutes prior to testing.

* p < 0.05 compared to saline control.

A single 5-mg/kg oral dose of Compound 60 produced a time-dependent reduction in the duration of immobility in the mouse TST (Table VII), with the peak effect occurring 60 minutes post-dosing. In two independent experiments, Compound 60 produced a dose-dependent reduction in the duration of immobility in the mouse TST when administered as a single oral dose 1 hour prior to testing (Tables VIII and IX). Imipramine, 15 mg/kg i.p., administered 30 minutes prior to testing, was used as a positive control in one of these studies (Table VIII).

10

Table VII. Compound 60 produced a time-dependent reduction in the duration of immobility in the mouse TST.

Time (post-dose)	Mean duration of immobility (sec)	SEM	n
0 (saline control)	154.9	10.0	13
0.5	84.9*	12.4	6
1	74.7*	10.5	6
2	93.0*	18.8	6
4	109.7	9.0	6
6	125.5	20.8	5
24	177.7	21.0	5
imipramine	103.6*	16.9	8

Compound 60 administered as a single dose, 5 mg/kg p.o.

15 Imipramine administered as a positive control, 15 mg/kg i.p. 30 minutes prior to testing.

* p < 0.05 compared to saline control.

Table VIII. Compound 60 produced a dose-dependent reduction in the duration of immobility in the mouse TST (experiment #1).

Dose (mg/kg)	Duration of Immobility (sec)	SEM	n
0 (saline control)	210.1	6.0	5
2.5	130.7*	11.2	4
5	123.5*	27.8	3
10	47.8*	16.8	6
imipramine	133.9*	17.4	4

Compound 60 administered as a single oral dose 60 minutes prior to testing.

Imipramine administered as a single dose, 15 mg/kg i.p., 30 minutes prior to testing.

5 * p < 0.05 compared to saline control.

Table IX. Compound 60 produced a dose-dependent reduction in the duration of immobility in the mouse TST (experiment #2).

Dose (mg/kg)	Duration of Immobility (sec)	SEM	n
0 (saline control)	149.1	15.3	8
0.625	143.3	13.0	6
1.25	125.8	9.7	8
2.5	69.6*	17.4	8
5	69.5*	19.8	6
10	15.6*	7.8	6

Compound 60 administered as a single oral dose 60 minutes prior to testing.

10 * p < 0.05 compared to saline control.

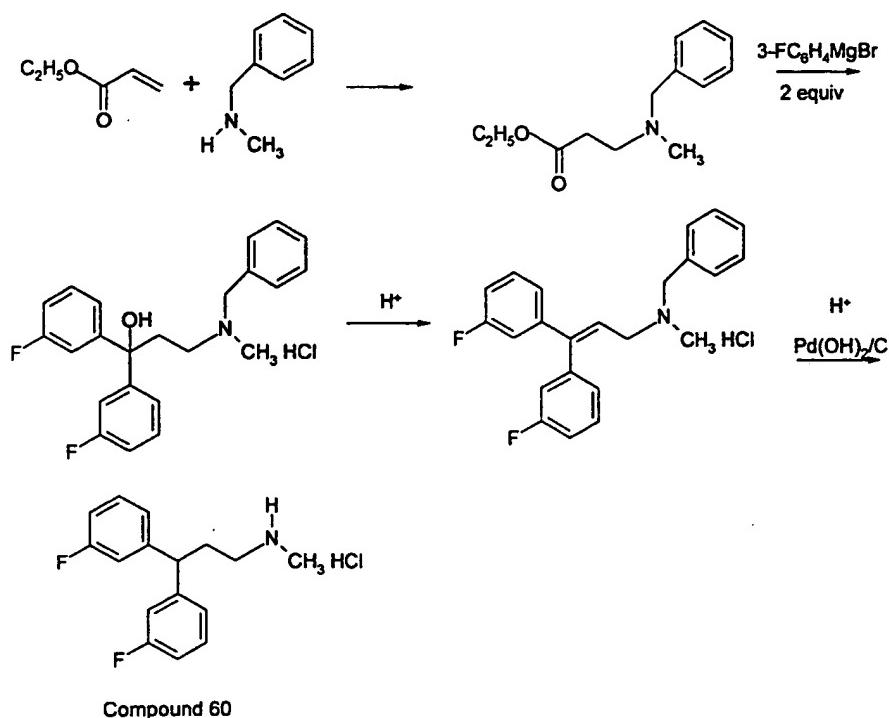
Example 3: Compound Synthesis

The different compounds described herein can be produced
15 using techniques well known in the art. This example illustrates
the use of such techniques to obtain different types of

compounds. Other particular compounds described herein can be readily obtained using well-known synthetic techniques, including modifying the procedure described below.

Capillary gas chromatographic and low-resolution electron-
5 impact mass spectral (EI-MS) data were obtained using a Hewlett-
Packard (HP) 5890 Series II Gas Chromatograph coupled to an HP
5971 Series Mass Selective Detector [Ultra-2 Ultra Performance
Capillary Column (crosslinked 5% PhMe silicone); column length,
25 m; column i.d., 0.20 mm; Helium flow rate, 60 mL/min;
10 injector temp., 250 °C; temperature program, 20 °C/min from 125
to 325 °C for 10 min, then held constant at 325 °C for 6 min].
Thin-layer chromatography was performed using Analtech Uniplate
250-μm silica gel HF TLC plates. UV light in conjunction with
ninhydrin and Dragendorff's spray reagents (Sigma Chemical Co.)
15 were used for detecting compounds on the TLC plates. Reagents
used in reactions were purchased from the Aldrich Chemical Co.
(Milwaukee, WI), Sigma Chemical Co. (Saint Louis, MO), Fluka
Chemical Corp. (Milwaukee, WI), Fisher Scientific (Pittsburgh,
PA), TCI America (Portland, OR), or Lancaster Synthesis (Windham,
20 NH).

Reaction Scheme 1: Synthesis of Compound 60



Compound 60 was synthesized from commercially available starting materials in the following four-step reaction sequence.

- 5 The first intermediate in this synthetic route, ethyl-N-benzyl-N-methyl-3-aminopropionate, was prepared by conjugate addition of N-benzylmethylamine to ethyl acrylate. The ester functionality of the first intermediate was then reacted with two equivalents of Grignard reagent (prepared from 1-bromo-3-fluorobenzene) to
- 10 provide N-benzyl-N-methyl-3-hydroxy-3-(bis-3-fluorophenyl)-propylamine. The Grignard reaction product was then dehydrated in a mixture of 6 M HCl/acetic acid to yield N-benzyl-N-methyl-3,3-bis(3-fluorophenyl)-allylamine. Catalytic hydrogenation of this material as its hydrochloride salt in ethanol over
- 15 Pearlman's catalyst [Pd(OH)₂/C] provided, after recrystallization from ethyl acetate, colorless, needles of Compound 60 hydrochloride.

Ethyl N-benzyl-N-methyl-3-aminopropionate.

In a 500-mL, 3-necked flask equipped with thermometer, reflux condenser, and a 125-mL addition funnel [charged with ethyl acrylate (88.3 mL, 81.5 g, 0.815 mol)] was placed *N*-benzylmethylamine (100 mL, 94.0 g, 0.776 mol). The ethyl acrylate was added dropwise to the stirring reaction mixture over a period of 80 min. After stirring for 18 h at room temperature, the product was vacuum distilled and the fraction containing product was collected at 78-95 °C (0.12-0.25 mm Hg), (138 g, 80% yield): bp 78-95 °C (0.12-0.25 mm Hg); TLC, R_f = 0.23 [hexane-EtOAc (5:1)], R_f = 0.57 [MeOH-CHCl₃ (100:5)]; GC, t_R = 6.06 min; EI-MS, 221 (M^+), 206 (M-CH₃), 192 (M-C₂H₅), 176 (M-OC₂H₅), 144 (M-C₆H₅), 134 [CH₂N(CH₃)CH₂Ph], 120 [N(CH₃)CH₂Ph], 91 (C₇H₇), 77 (C₆H₅), 42 (CH₂CH₂N); ¹H NMR (free base, CDCl₃) δ 1.25 ppm (t, J = 7.1, 3H, CH₂CH₃), 2.20 (s, 3H, NCH₃), 2.51 (t, J = 7.3, 2H, COCH₂), 2.74 (t, J = 7.2, 2H, CH₂N), 3.51 (s, 2H, NCH₂Ph), 4.13 (q, J = 7.1, 2H, OCH₂CH₃), 7.18-7.35 (m, 5H, ArH); ¹³C NMR (free base, CDCl₃) δ 15.2 (CH₂CH₃), 34.0 (COCH₂), 42.9 (NCH₃), 53.8 (NCH₂), 61.4 (OCH₂CH₃), 63.1 (CH₂Ph), 128.0 (CH), 129.2 (CH), 130.0 (CH), 139.9 (q), 173.7 (q).

20

N-Benzyl-*N*-methyl-3-hydroxy-3-bis(3-fluorophenyl)propylamine hydrochloride.

In a 5-L, four-necked, round-bottom flask, under nitrogen, was placed Mg [51.5 g, 2.12 mol, turnings, washed with THF (2 x 300 mL)] and THF (2 L). An addition funnel was charged with 3-bromofluorobenzene (neat, 392.8 g, 2.24 mol). One-twentieth of the bromide was added to the magnesium suspension followed by one crystal of iodine. After initiation of the Grignard reaction the remaining 3-bromofluorobenzene was then added to the refluxing mixture over a period of 50 min. The reaction was refluxed for an additional 45 min. To the refluxing solution of Grignard reagent was added a solution of ethyl *N*-benzyl-*N*-methyl-3-aminopropionate (187.5 g, 0.847 mol) in THF (100 mL) over a

period of 20 min. After the ester addition was complete, the reaction was refluxed for 1 h. The reaction was then cooled in an ice bath. Saturated NH₄Cl (aq., 400 mL) and H₂O (400 mL) were added and the mixture was transferred to a separatory funnel.

5 The organic layer was separated and the aqueous layer was extracted once with THF (400 mL). The combined organic layers were washed with satd. NaCl (aq., 2 x 200 mL), dried (anh. Na₂SO₄), filtered through paper, and rotary evaporated vacuum to yield 281.6 g (90%) of crude product as an orange, viscous oil.

10 This material (281.6 g, 0.766 mol) was dissolved in acetonitrile (1.4 L). Concentrated hydrochloric acid (65.0 mL, 0.786 mol, 12 M) was added to the stirring filtrate. The crystallizing mixture was then cooled to -20 °C for 17 h. The product was collected, washed with cold acetonitrile (800 mL), and dried to

15 provide a white solid, 235.6 g (69% yield from the ester).

For analytical purposes, the hydrochloride salt was further purified by recrystallization from acetonitrile: Mp 194-197 °C (uncorr.); TLC, R_f = 0.23 [hexane-EtOAc (5:1)], R_f = 0.85 [MeOH-CHCl₃ (100:5)], R_f = 0.72 [MeOH-CHCl₃ (100:3)]; GC, t_R =

20 10.93 min; MS, 367 (M⁺), 272 (M-C₆H₄F), 258 (M-CH₂Ph-H₂O), 219 [(C₆H₄F)₂CH], 148 [CH₂CH₂N(CH₃)CH₂Ph], 134 [CH₂N(CH₃)CH₂Ph], 91 (C₇H₇), 42 (CH₂CH₂N); ¹H NMR (free base, CDCl₃) δ 2.18 (s, 3H, NCH₃), 2.41 (m, 2H, CHCH₂), 2.58 (m, 2H, CH₂N), 3.42 (s, 2H, CH₂Ph), 6.86 (dt, J₁ = 8.5, J₂ = 1.8, 2H, Ar-H), 7.18-7.30 (m,

25 10H, Ar-H), 8.33 (bs, 1H, OH); ¹³C NMR (free base, CDCl₃) δ 35.6 (CHCH₂), 41.5 (CH₃, NCH₃), 54.3 (CH₂, CH₂N), 62.6 (CH₂, CH₂Ph), 113.1 (d, J = 23, CH, Ar-C₅,_{5'}), 113.5 (d, J = 23, CH), 121.2 (d, J = 3, CH), 127.5 (CH), 128.5 (CH), 129.2 (CH), 129.5 (CH), 129.6 (CH), 137.0 (q), 150.2 (q), 162.8 (d, J = 243, q, Ar-C₃,_{3'}).

30

N-Benzyl-N-methyl-3-bis(3-fluorophenyl)allylamine hydrochloride.

In a 5-L, 3-necked reaction vessel, equipped with an overhead mechanical stirrer, reflux condenser, and thermometer,

was placed *N*-benzyl-*N*-methyl-3-hydroxy-3-bis(3-fluorophenyl)propylamine hydrochloride (225.4 g, 0.559 mol), 6 M HCl (1392 mL), and glacial HOAc (464 mL). The suspension was heated in a water bath (80-85 °C) and stirred for 18 h. After 18
5 h of heating, the reaction mixture was cooled in an ice/MeOH bath. Ethyl acetate (500 mL) was added to the cooled reaction mixture. NaOH (10 M, 1.7 L) was then added to the cooled mixture over a period of 25 min at such a rate as to keep the temperature below 40 °C. The mixture was transferred to a 6-L separatory
10 funnel. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were washed with satd. NaCl (aq., 2 x 100 mL), dried (Na₂SO₄, 250 g), rotary evaporated, and then dried under vacuum to provide 185.6 g (95% yield) of the free base as a
15 fluid, brownish-colored oil.

The material above was stirred with hexane (1.5 L). The resulting solution was filtered through paper. 4 M HCl in dioxane (146 mL) was added dropwise with stirring to the filtrate over a period of 5 min. The semi-translucent solvent was then
20 decanted away from the light-yellow colored, semisolid precipitate. The crude hydrochloride salt was dissolved in refluxing ethyl acetate (600 mL) and was filtered. The filtrate was then thoroughly cooled in an ice bath, and hexane (110 mL) was slowly added with vigorous stirring. After cooling in an ice
25 bath for 2 h, the entire flask filled with a white crystalline solid. This material was collected on a filter funnel, washed with ice-cold hexane/ethyl acetate [(1:4), 400 mL], and dried to yield 128.7 g, 59.7% of a white solid. On standing the mother liquor precipitated another 14.8 g of an off-white solid. Total
30 yield 128.7 g + 14.8 g = 143.5 (67%). Mp 141-142 °C (uncorr.); TLC, R_f = 0.20 [hexane-EtOAc (5:1)], R_f = 0.75 [MeOH-CHCl₃ (100:5)], R_f = 0.49 [MeOH-CHCl₃ (100:3)]; GC, t_R = 10.40 min; MS, 349 (M⁺), 330, 301, 281, 258 (M-CH₂Ph), 240, 229 [M-N(CH₃)CH₂Ph], 201, 183, 146, 133, 109, 91 (CH₂C₆H₅), 65, 42

(CH₂NHCH₃); ¹H NMR (free base, CDCl₃) δ 2.20 ppm (s, 3H, NCH₃), 3.08 (d, J = 6.8, 2H, CH₂N), 3.47 (d, J < 1, 2H, CH₂Ph), 6.29 (t, J = 6.8, 1H, CH), 6.85-7.04 (m, 6H, ArH), 7.19-7.35 (m, 7H, ArH).

5

N-Methyl-3,3-bis(3-fluorophenyl)propylamine hydrochloride.

N-Benzyl-N-methyl-3-bis(3-fluorophenyl)allylamine hydrochloride (120.0 g, 0.311 mol) was dissolved in abs. EtOH (1250 mL). Pd(OH)₂/charcoal (Fluka[®], ~20% Pd, 10.0 g) was added. 10 The reaction mixture was stirred under a steady flow of hydrogen gas for 18 h at 25 °C (atmospheric pressure). The mixture was then filtered through Celite[®]/fritted glass, the catalyst was washed with EtOH (2 x 50 mL), and the solvent was removed under reduced pressure to yield 95.4 g, 103% of crude product. This 15 material was dissolved in refluxing ethyl acetate (300 mL) with vigorous stirring and filtered. The flask was allowed to stand for 2 h at 25 °C, during which time the hydrochloride salt began to crystallize as needles. The flask was then cooled, the product was collected, washed with ice-cold ethyl acetate 20 (20 mL), and dried to yield 73.7 g, 80% of Compound 60 as a white, crystalline solid.

Mp 129-130 °C; UV/Vis, ε = 2.1 × 10³ L·mol⁻¹·cm⁻¹ (264 nm, EtOH, 25 °C, linear range: 0.05-0.20 mg/mL); TLC, R_f = 0.00 [hexane-EtOAc (5:1)], R_f = 0.07 [MeOH-CHCl₃ (100:5)], R_f = 0.19 25 [MeOH-CHCl₃-NH₄OH (100:5:1)]; GC, t_R = 7.45 min; MS, 261 (M⁺), 229, 215, 201, 183, 164, 150, 138, 122, 101, 83, 75, 57, 42 [CH₂NHCH₃]; ¹H NMR (HCl salt, CDCl₃ + 1 gtt MeOD) δ 2.56 ppm (m, 2H, NCH₂), 2.60 (s, 3H, NCH₃), 2.85 (t, J = 8.0, 2H, CHCH₂), 4.11 (t, J = 8.0, 1H, CH), 6.87-6.98 (m, 4H, ArH), 7.06 (d, J = 30 7.7, 2H, Ar₂,_{2'}H), 7.25 (dd, J₁ = 6, J₂ = 8, ArH); ¹³C NMR (HCl salt, CDCl₃ + 1 gtt MeOD) δ 30.9 (CH₂, CHCH₂), 32.7 (CH₃, NCH₃), 47.6 (CH, CHCH₂), 47.8 (CH₂, CH₂N), 113.9 (J = 21, ArC₂,_{2'} or

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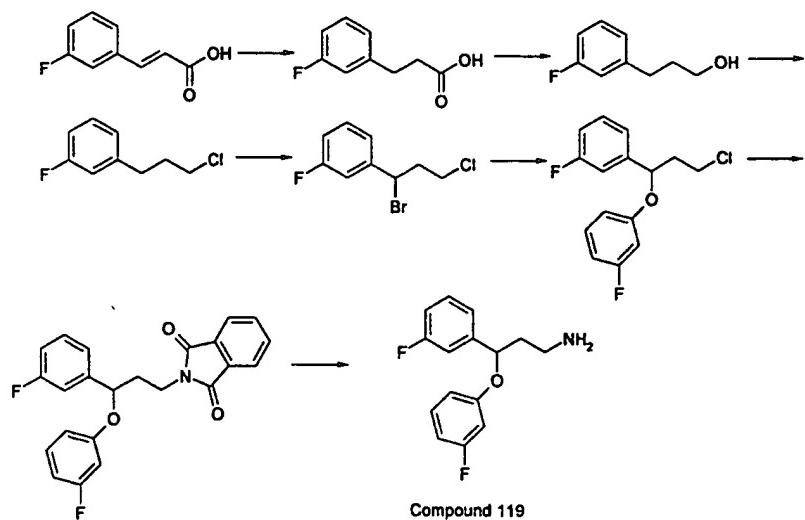
$\text{ArC}_4,4'$), 114.5 (d, $J = 22$, $\text{ArC}_2,2'$ or $\text{ArC}_4,4'$), 123.2 (d, $J = 3$, $\text{Ar-C}_6,6'$), 130.3 (d, $J = 9$, $\text{Ar-C}_5,5'$), 144.7 (d, $J = 7$, $\text{Ar-C}_1,1'$), 162.9 (d, $J = 245$, $\text{Ar-C}_3,3'$); IR: KBr pellet, (cm^{-1}) 3436.9, 2963.4, 2778.5, 2453.7, 1610.6, 1589.3, 1487.0, 1445.3,
 5 1246.0, 764.5; solubility: 2 g/mL (H_2O), 1 g/mL (EtOH); anal.
 calcd. for $\text{C}_{16}\text{H}_{17}\text{NF}_2 \cdot \text{HCl}$ (Karl Fischer: 0.26% H_2O): C, 64.37; H, 6.11; N, 4.69; found: C, 64.14; H, 6.13; N, 4.69.

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Reaction Scheme 2: Synthesis of Compound 119.



Compound 119 was synthesized in a seven-step reaction sequence starting from commercially-available *trans*-3-fluorocinnamic acid. This synthetic route is conceptually similar to that reported in the literature (U.S. Patent 4,313,896 (1982) hereby incorporated by reference herein) for related analogs. However, the three final steps were performed using a significantly different reaction sequence than that reported. The cinnamic acid was reduced and chlorinated in three steps to the corresponding 3-(3-fluorophenyl)propylchloride. This compound was brominated with NBS (*N*-bromosuccinimide) and the resulting trihalide was then reacted with 3-fluorophenol. The resulting ether was converted to the final product using a Gabriel synthesis.

15

3-Fluorohydrocinnamic acid.

Trans-3-fluorocinnamic acid (25.0 g, 150.4 mmol) was dissolved in abs. EtOH (250 mL) and hydrogenated over 10% Pd/C (2.5 g) in a Parr apparatus at 60 psig, 50 °C, for 1 h (hydrogen uptake: calcd. 245 psig; found 260 psig). The reaction mixture was filtered and evaporated to yield a crystalline product (23.0 g, 89%). GC, t_R = 4.43 min; MS, 168 (M^+).

3-(3-Fluorophenyl)-1-propanol.

Under a stream of dry nitrogen, at 0-10 °C, a solution of 3-fluorohydrocinnamic acid (22.0 g, 131 mmol) in THF (100 mL) was added dropwise, over a period of 15 min, to a suspension of LiAlH₄ (4.23 g, 111 mmol) in THF (200 mL). The reaction was heated to reflux for a period of 1 h and then worked-up according to Fieser & Fieser's Reagents for Organic Synthesis (vol. 1, 1967) to provide a white solid (20.1 g, 99%). GC, t_R = 3.74 min; MS, 154 (M^+).

3-(3-Fluorophenyl)-1-propylchloride.

A solution of 3-(3-fluorophenyl)-1-propanol (15.0 g, 97.4 mmol) and triphenylphosphine (36.0 g, 137.3 mmol) in CCl_4 (150 mL) was refluxed for 19 h. Additional $\text{P}(\text{C}_6\text{H}_5)_3$ (3 x 3.0 g, 3 x 11.4 mmol) was added periodically over a period of 24 h. The 5 resulting precipitate was removed by filtration and the solids were washed with hexane. The filtrate was evaporated under vacuum and the residue was suspended in hexane (200 mL) and then filtered. Evaporation of the filtrate provided 16.0 g (95.1%) of crude product which was purified by silica gel flash 10 chromatography, elution with hexane, to provide 14.7 g (87%) of a colorless liquid. GC, t_R = 3.63 min; MS, 172/174 (M^+).

3-Bromo-3-(3-fluorophenyl)-1-propylchloride.

A solution of the above chloride (12.0 g, 69.5 mmol), *N*-bromosuccinimide (17.3 g, 97.2 mmol), and dibenzoyl peroxide (0.06 g) in CCl_4 (75 mL) was refluxed for 1 h. The reaction mixture was then cooled in an ice bath, filtered, and the solids were washed with hexane. The filtrate was evaporated to provide 17.9 g (100%) of product. GC, t_R = 5.21 min; MS, 251/253 (M^+).
20

3-(3-Fluorophenoxy)-3-(3-fluorophenyl)-1-propylchloride.

A mixture of 3-bromo-3-(3-fluorophenyl)-1-propylchloride (4.0 g, 15.9 mmol), 3-fluorophenol (1.98 g, 17.7 mmol), and K_2CO_3 (2.65 g, 19.2 mmol) suspended in acetone (80 mL) was refluxed for 25 15 h. The volatiles were then removed under vacuum and the resulting residue was suspended in a mixture of hexane (200 mL) and NaOH (0.1 M, 100 mL). The layers were separated and the organic layer washed, 0.1 M NaOH (100 mL) and H_2O (100 mL), dried (anh. Na_2SO_4), and evaporated *in vacuo*. The resulting residue 30 was chromatographed on silica gel, elution with hexane followed by hexane/EtOAc [100:1] then [40:1] to provide 1.64 g (37%) of product as a colorless oil. GC, t_R = 7.28 min; MS, 282/283 (M^+); TLC r_f = 0.3, hexane/EtOAc [40:1].

N-Phthaloyl-3-(3-fluorophenoxy)-3-(3-fluorophenyl)-1-propylamine.

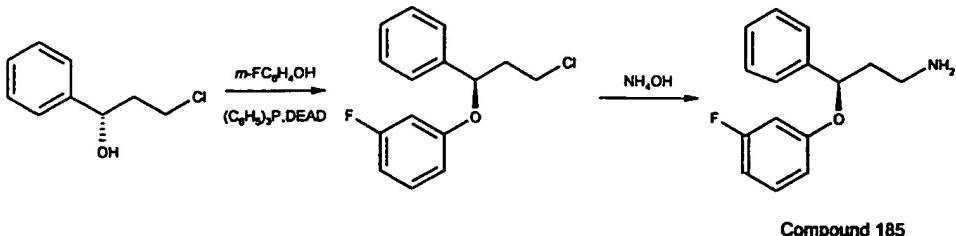
A solution of 3-(3-fluorophenoxy)-3-(3-fluorophenyl)-1-propylchloride (1.52 g, 5.38 mmol) and potassium phthalate (1.20 g, 6.48 mmol) was heated to 90 °C in DMF (30 mL) for a period of 5 2 h in a nitrogen atmosphere. The reaction mixture was then cooled and poured into H₂O (100 mL). The resulting solution was extracted with Et₂O (2 x 100 mL). The organic extract was washed, satd. aq. NaCl (100 mL) and H₂O (2 x 100 mL), dried (anh. Na₂SO₄), and evaporated under vacuum to provide 2.17 g of crude 10 product. The material was chromatographed on silica gel, elution with hexane/EtOAc [40:1] and then [20:1] to provide after evaporation 1.81 g (86%) of product as a glass.

3-(3-Fluorophenoxy)-3-(3-fluorophenyl)-1-propylamine.

15 A solution of N-phthaloyl-3-(3-fluorophenoxy)-3-(3-fluorophenyl)-1-propylamine (1.74 g, 4.42 mmol) and anh. hydrazine (1.43 g, 44.6 mmol) in abs. EtOH (30 mL) was refluxed for 1 h. The reaction was cooled and evaporated under vacuum. The resulting material was suspended in Et₂O (75 mL) and washed 20 with 0.2 M NaOH (2 x 25 mL). The organic layer was dried (anh. Na₂SO₄) and evaporated under vacuum to provide 1.04 g (89.3%) which was purified by reverse-phase chromatography [Vydac Prep. C18; 264 nm; 50 mL/min; gradient elution ACN/0.1% HCl aq., 10%-50% over 20 min; *r*_t = 17.4 min], to yield 0.89 g (67%) of 25 Compound 119 as a hygroscopic hydrochloride salt.

In a similar manner, Compound 236 can be synthesized using the previously described synthetic protocol with the following substitution: 4-trifluorophenol material substituted in Reaction scheme 2 for 3-fluorophenol.

51



Compound 185 was prepared following a similar procedure for the chiral synthesis of fluoxetine (Brown, H.C. et al., *J. Org. Chem.* 53(13), 2916-2920(1988)).

5

(R)-3-(3-fluorophenoxy)-3-phenylpropylchloride.

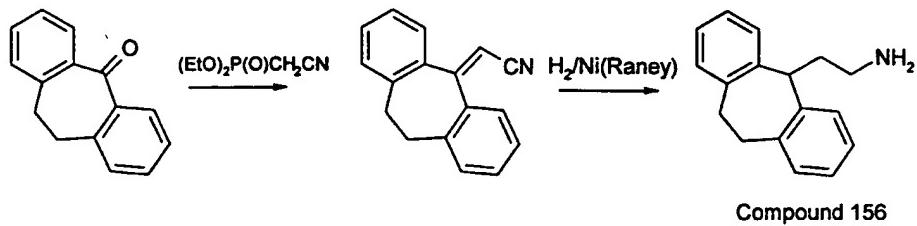
A solution of (*S*)-(-)-3-chloro-1-phenyl-1-propanol (4.00 g, 23.4 mmol), 3-fluorophenol (2.63 g, 23.4 mmol), and diethyl azodicarboxylate (4.00 g, 23.4 mmol) was dissolved in THF (200 mL). The mixture was cooled to 0 °C and triphenylphosphine (6.77 g, 25.8 mmol, 1.1 equiv) was added slowly over 10 min. The reaction mixture was then stirred at room temperature for 18 h. The THF was subsequently evaporated under vacuum to afford a gel which was washed with pentane (3 x 50 mL). The pentane washings were filtered and the filtrate was evaporated under vacuum to give a clear oil. This oil was dissolved in diethyl ether (150 mL) and washed with 1% HCl/satd. aq. NaCl (25 mL), 0.1 M NaOH/satd. aq. NaCl (2 x 25 mL), and finally H₂O (2 x 25 mL). The organic layer was then dried (anh. Na₂SO₄), filtered, and evaporated to dryness under vacuum to give an oil. The crude product was chromatographed on silica gel, elution with 40:1 hexane-EtOAc, to provide 971 mg (15.7%) of product as a colorless oil.

25 (R)-3-(3-Fluorophenoxy)-3-phenylpropylamine.

A solution of (*R*)-3-(3-fluorophenoxy)-3-phenylpropyl chloride (0.971 g, 3.96 mmol), conc. NH₄OH (30 mL), and EtOH (20 mL) was shaken at 90 °C on a Parr® apparatus (50-90 psig) for 18 h. The mixture was then evaporated under vacuum and the residue

was dissolved in Et₂O (100 mL) and washed with H₂O (2 x 25 mL). The organic layer was dried (anh. Na₂SO₄), filtered, and evaporated under vacuum to provide an oil. This material was then dissolved in EtOAc (50 mL) and filtered. A solution of 5 maleic acid (0.272 g, 2.6 mmol, 0.93 equiv) dissolved in hot EtOAc (5 mL) was added to precipitate Compound 185 as its white solid maleate salt (519 mg, 53.5%): TLC R_f 0.25 (1% MeOH/CHCl₃); GC, t_r 7.37 min; EI-MS, m/z 245 (M⁺).

10

Reaction Scheme 4: Synthesis of Compound 1565-Cyanomethylidino-10,11-dihydrodibenzo[a,d]cycloheptene.

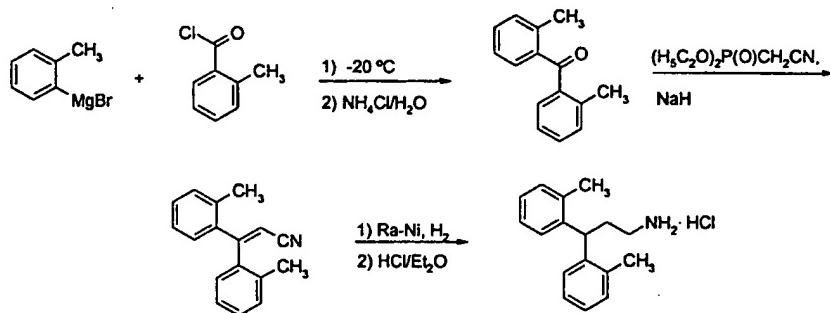
To a solution of diethyl cyanomethylphosphonate (9.66 g, 54.5 mmol) in dry N,N-dimethylformamide (DMF, 40 mL) was added 15 NaH (60% dispersion, 2.20 g, 55.0 mmol) over a period of 2 min. The reaction was stirred for 10 min and then a solution of dibenzosuberone (10.3 g, 49.6 mmol) in dry DMF (10 mL) was added over a period of 2 min. The reaction was stirred at 80 °C for 4 h under N₂. Water (200 mL) was added and the reaction mixture 20 was extracted with Et₂O (2 x 100 mL). The combined organic layers were rotary evaporated to less than 50 mL. The resulting crystals were collected and washed with cold Et₂O (2 x 50 mL) to yield 7.48 g (65.3%) of product.

25 5-(2-Aminoethyl)-5H-10,11-dihydrodibenzo[a,d]cycloheptene hydrochloride.

The conjugated nitrile from above was dissolved in EtOH (100 mL). 1 M NaOH (10 mL) and Raney® nickel (aq. suspension, 0.50 g) were added. The reaction mixture was shaken under 60

psig H₂ at 50 °C for 22 h, and was then filtered through Celite®. The filtrate was rotary evaporated and the residue was dissolved in Et₂O (100 mL) and washed with satd. aq. NaCl (50 mL) and H₂O (50 mL). The Et₂O layer was dried (anh. Na₂SO₄) and rotary evaporated to give the crude product (850 mg) as a colorless oil. This oil was dissolved in EtOAc (5 mL) and filtered. 1.0 M HCl in Et₂O (5 mL) was added to the filtrate and a white, crystalline solid precipitated. This material was recrystallized from EtOH (5 mL)/Et₂O (12 mL) to yield 600 mg (50.7%) of Compound 156 as a white powder.

Synthesis of Compound 65



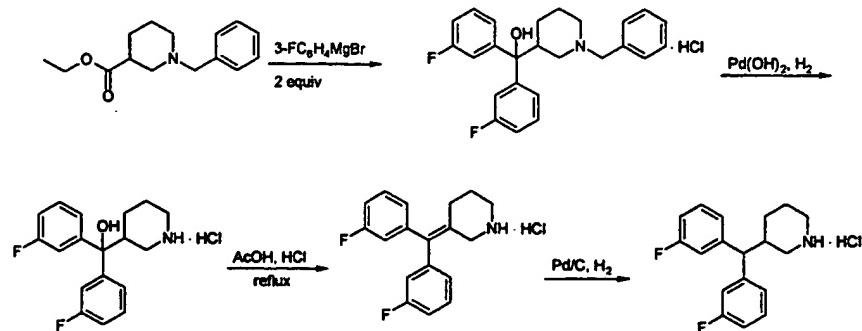
o-Toluoyl chloride (31.0 g, 201 mmol) in diethyl ether (50 mL) was added over a period of 10 min to o-tolylmagnesium bromide (2.0 M in diethyl ether; 105 mL, 210 mmol) cooled to -20 °C in a methanol/ice bath. The cold bath was then removed. A voluminous amount of precipitate formed in the reaction mixture. After stirring 10 min, satd. aq. NH₄Cl (200 mL) was carefully added over a period of 8 min. The organic layer was separated. The aqueous layer was extracted with diethyl ether (50 mL). The combined organic layers were washed with H₂O (2 x 50 mL), dried (anh. Na₂SO₄), and rotary evaporated to yield 41.6 g (98.7%) of product.

Sodium hydride (60% in mineral oil; 3.2 g, 1.9 g NaH, 80 mmol) was added to a solution of diethyl cyanomethylphosphonate (14.2 g, 80.2 mmol) in DMF (75 mL) over a period of 2 min. The reaction mixture was stirred at 80 °C for 5 30 min. 2,2'-dimethylbenzophenone (15.2 g, 72.3 mmol) in DMF (15 mL) was then added to the reaction mixture over a period of 2 min. The reaction mixture was stirred at 80 °C. At 27 h H₂O (300 mL) was added to the reaction mixture. This mixture was extracted with diethyl ether (2 x 100 mL). The combined organic 10 layers were washed with H₂O (2 x 100 mL), dried (anh. Na₂SO₄), and rotary evaporated to give 15.96 g. The resulting oil was flash chromatographed (step gradient: hexanes; 40:1 hex/EtOAc; 20:1 hex/EtOAc) through flash silica gel (250 x 50 mm) to yield 6.33 g of product.

15 This material (6.33 g) was dissolved in EtOH (300 mL). Raney nickel (Fluka[®]; ~50% slurry in H₂O; 3.2 g in 1 M NaOH) was added to the filtrate. The reaction mixture was shaken under 60 psig H₂ at 60 °C for 18 h. The reaction mixture was then filtered through paper and the filtrate was rotary evaporated. 20 This material was dissolved in diethyl ether (100 mL) and washed with H₂O (2 x 50 mL). The organic layer was dried (anh. Na₂SO₄) and rotary evaporated to yield 5.61 g of product. This oil was dissolved in EtOAc (60 mL). The HCl salt of the amine was formed by adding 1.0 M HCl in diethyl ether (30 mL). More diethyl ether 25 (30 mL) was added to the mixture. The precipitate was collected and washed with diethyl ether (2 x 50 mL). The resulting white solid was recrystallized from EtOH (60 mL)/diethyl ether (120 mL) to yield 3.32 g of the crystalline hydrochloride salt.

Synthesis of Compound 111

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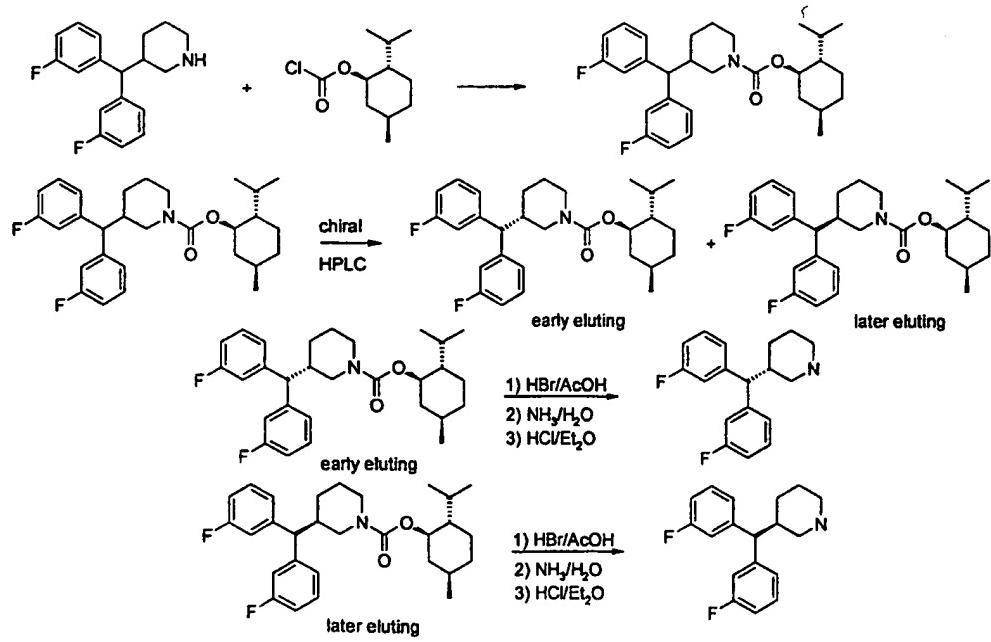


3-Bromofluorobenzene (15.00 g) and magnesium turnings (1.95 g) were dissolved in anh. THF (150 mL). The reaction mixture was refluxed under nitrogen for 30 min. racemic-Ethyl N-benzylnipecotate (8.00 g, 32.3 mmol) in anh. THF (10 mL) was added over a period of 1 min. The reaction mixture was refluxed for 1.5 h and was then allowed to cool. Satd. aq. NH₄Cl (50 mL) was added and the mixture was transferred to a separatory funnel containing satd. aq. NaCl (250 mL) and diethyl ether (150 mL). The organic layer was separated, washed with H₂O (50 mL), dried (anh. Na₂SO₄), and rotary evaporated to give 13.0 g of amine. This material was flash chromatographed (gradient: hexanes, 20:1 hex/EtOAc, 9:1 hex/EtOAc, 4:1 hex/EtOAc) through flash silica gel. The fractions containing only product were combined. To this solution was added 1.0 M HCl in diethyl ether (40 mL). This solution was then rotary evaporated and dried under high vacuum to yield 10.93 g (78.6%) of product.

The intermediate prepared above (10.73 g, 24.96 mmol) was dissolved in EtOH (200 mL). Pearlman's catalyst (Fluka[®]; ~20% Pd; 2.15 g) was added. The reaction mixture was shaken under 50 psig H₂ at 50 °C for 2 h. The reaction mixture was then filtered through Celite, and the filtrate was rotary evaporated to yield 8.15 g (96.1%) of product. The intermediate prepared above (7.64 g, 22.5 mmol) was dissolved in glacial acetic acid (75 mL). Conc. aq. HCl (75 mL) was added. The reaction mixture

was refluxed under N₂ flow for 5 h. The reaction mixture was then rotary evaporated to give 7.03 g (97.2%) of product. This solid was dissolved in refluxing ethanol (70 mL). This solution was filtered, more diethyl ether (210 mL) was added, and the resulting crystals were filtered, washed with diethyl ether (2 x 50 mL), and dried under high vacuum to yield 6.27 g (86.7%) of product. The intermediate alkene prepared above (5.66 g, 17.6 mmol) was dissolved in ethanol (200 mL). Palladium on charcoal (~10% Pd; 1.13 g) in H₂O (5 mL) was added. The reaction mixture was shaken under 60 psig H₂ at 60 °C for 16.5 h. The reaction mixture was filtered through Celite, and the filtrate was rotary evaporated to give 5.54 g of product. This material was crystallized from ethanol (10 mL)/diethyl ether (40 mL). The crystals were filtered, washed with diethyl ether (2 x 50 mL), and dried under high vacuum to yield 4.82 g (84.6%) of product.

Synthesis of Compound 216 and Compound 217



(--)-Menthyl chloroformate (1.57 mL, 1.60 g, 7.32 mmol) was added to a solution of racemic-3-[bis(3-fluorophenyl)methyl]piperidine (2.10 g, 7.31 mmol) and triethylamine (3.1 mL, 22 mmol) dissolved in CH₂Cl₂ (40 mL). After 5 min the reaction solution was rotary evaporated. This material was then flash chromatographed (9:1 hex/EtOAc) through flash silica gel to yield 2.90 g (84.5%) of product.

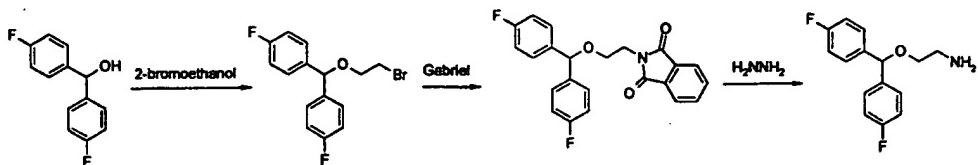
The resulting oil (2.90 g) was separated on chiral stationary-phase HPLC (Chiralcel OD; column: 20 x 250 mm; eluent: 19:1 hexanes/isopropanol; flow rate: 10 mL/min; load: 1 mL of 50 mg/mL; detector: 254 nm). Rotary evaporation yielded 1.28 g (44.1%) of the early diastereomer and 1.24 g (42.8%) of the late for a total yield of 86.9%. Analytical HPLC showed >99.5% purity for the early diastereomer and >99.0% purity for the late diastereomer.

The early eluting diastereoisomer (959 mg, 2.04 mmol) was dissolved in 30% HBr in acetic acid (20 mL). The reaction solution was stirred at 80 °C for 14 h. Ice (~20 g) was added to the reaction mixture followed by H₂O (20 mL), conc. aq. NH₄OH (29%, 10 mL), and satd. aq. NaHCO₃ (10 mL). This mixture was extracted with CHCl₃ (2 x 30 mL). The combined organic layers were washed with satd. aq. NaHCO₃ (30 mL), dried (anh. Na₂SO₄), and rotary evaporated to give 921 mg of crude product. The resulting oil was flash chromatographed (gradient elution: CHCl₃, 1:10 MeOH/CHCl₃, 0.03:1:10 NH₃/MeOH/CHCl₃) through flash silica gel. Fractions containing product were combined and rotary evaporated to yield 610 mg (104%) of an oil. This material was dissolved in CHCl₃ (10 mL) and washed with 1 M NaOH (10 mL). The organic layer was dried (anh. MgSO₄) and rotary evaporated to give 421 mg (71.7%) of product. This material was dissolved in EtOAc (2.0 mL). A solution of 1.0 M HCl in diethyl

ether (3.0 mL) was added. Diethyl ether (1.0 mL) was added, and the crystallizing solution was heated to clearness and then allowed to stand. The resulting crystals were washed with diethyl ether (2 x 5 mL) and dried under high vacuum to yield
5 415 mg (62.8%) of product as a crystalline solid.

The later eluting diastereoisomer (1.24 g, 2.64 mmol) was dissolved in 30% HBr in acetic acid (20 mL). The reaction solution was stirred at 80 °C for 16 h. Ice (~25 g) was added to the reaction mixture followed by H₂O (25 mL), conc. aq NH₃ (29%,
10 10 mL), and satd. aq. NaHCO₃ (10 mL). This mixture was extracted with CHCl₃, (2 x 30 mL). The combined organic layers were washed with 1 M NaOH (2 x 30 mL), dried (anh. Na₂SO₄), and rotary evaporated to give 1.07 g. This material was flash chromatographed (gradient elution: CHCl₃, 0.03:1:10
15 NH₃/MeOH/CHCl₃) through flash silica gel to yield 625 mg (82.4%) of amine. This material was dissolved in EtOAc (3.0 mL). A solution of 1.0 M HCl in diethyl ether (3.0 mL) was added. Diethyl ether (3.0 mL) was added, and the crystallizing solution was heated to clearness and then allowed to stand. The
20 supernatant was decanted and the resultant crystals were washed with diethyl ether (2 x 10 mL) and dried under high vacuum to yield 565 mg (66.1%) of product as a crystalline solid.

Synthesis of Compound 223 (Flunamine)



5 synthesis references: *Collect. Czech. Chem. Commun.* 49(11), 2649-2660(1984), *J. Med. Chem.* 35(22), 4238-4248(1992).

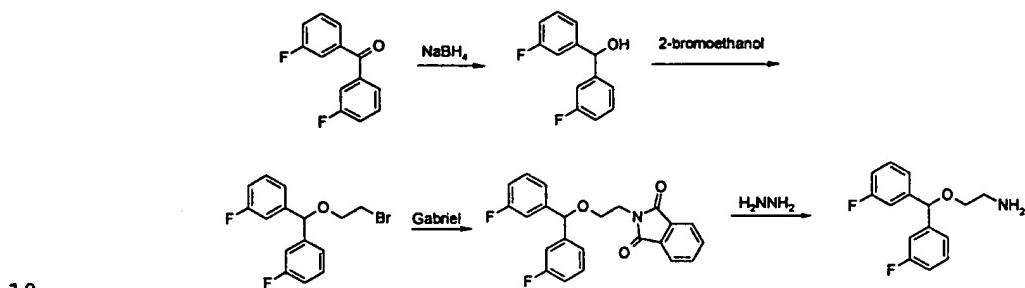
A solution of 4,4'-difluorodiphenylmethanol (12.5 g, 56.9 mmol), 2-bromoethanol (7.11 g, 56.9 mmol), conc. H₂SO₄ (2 drops) in toluene (100 mL) was refluxed for 1.5 h. The reaction 10 was then evaporated under vacuum. The residue was dissolved in diethyl ether (100 mL), washed with H₂O (2 x 25 mL), dried (anh. Na₂SO₄), and evaporated under vacuum to provide 18.62 g, 100% yield of crude bromide.

A solution of the bromide prepared above (18.62 g, 15 56.94 mmol) and potassium phthalimide (10.55 g, 56.94 mmol) in DMF (100 mL) was heated in an oil bath to 120 °C for 10 min. The reaction was then cooled to 25 °C, diethyl ether (400 mL) was added, and the mixture was washed with brine (5 x 100 mL), dried 20 (anh. Na₂SO₄), and then one-half of the solvent was evaporated under reduced pressure. The product crystallized from the evaporating solvent, was collected on a funnel, and dried to provide 13.0 g, 58% yield of colorless crystals.

To a suspension of the phthalimide prepared above (13.0 g, 33.1 mmol) in methanol (100 mL) was added anh. hydrazine 25 (5.2 mL, 5.3 g, 165 mmol). The reaction was heated at reflux for 30 min. The volatiles were then removed under vacuum. The residue was dissolved in a mixture of diethyl ether (300 mL), 1 M NaOH (50 mL), and H₂O (200 mL). The layers were separated and the organic layer was washed with 1 M NaOH (50 mL) and H₂O (50 30 mL), dried (anh. Na₂SO₄), and evaporated to give 6.7 g of an oil.

This oil, dissolved in EtOAc (20 mL), was added to a solution of maleic acid (2.98 g, 25.7 mmol) in hot EtOAc (40 mL). The maleate salt crystallized, was collected, washed with diethyl ether (20 mL), and dried under vacuum to provide 8.34 g colorless 5 crystals. GC/MS rt 6.93 min; EI-MS, m/z 264; TLC, 5% MeOH/CHCl₃, Rf 0.25.

Synthesis of Compound 218



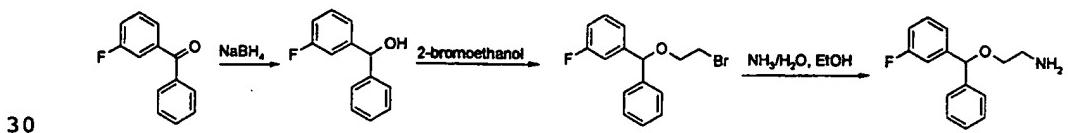
To a solution of 3,3'-difluorobenzophenone (15.0 g, 68.7 mmol) in ethanol (50 mL) was added sodium borohydride (2.86 g, 75.6 mmol). The reaction mixture was then heated to reflux for 15 min. The reaction was then cooled and the solvent evaporated under vacuum. The residue was dissolved in diethyl ether (100 mL), washed with H₂O (3 x 50 mL), dried (anh. Na₂SO₄), and evaporated to provide 11.61 g, 76.8% yield of product as an oil: TLC hex/EtOAc [10:1], Rf = 0.4.

A solution of 3,3'-difluorobenzhydrol (11.61 g, 52.8 mmol), 2-bromoethanol (7.26 g, 58.1 mmol), and conc. H₂SO₄ (2-drops) in toluene (100 mL) was refluxed for 1.3 h using a Dean-Stark trap to remove water. The reaction was then evaporated under vacuum. The residue was dissolved in diethyl ether (100 mL), washed with H₂O (2 x 25 mL), dried (anh. Na₂SO₄), and evaporated under vacuum to provide 17.28 g, 100% yield of crude bromide as an oil.

A solution of the crude bromide prepared above (17.28 g, 52.8 mmol) and potassium phthalimide (10.77 g, 58.13 mmol) in DMF (100 mL) was heated in an oil bath to 120 °C for 60 min. The reaction was then cooled to 25 °C, diethyl ether (400 mL) was added, and the mixture was washed with brine (100 mL), 1 M NaOH (100 mL), then brine again (3 x 100 mL), dried (anh. Na_2SO_4), and then most of the solvent was evaporated under reduced pressure. The product crystallized, was collected on a funnel, washed twice with hexane/ether [1:1], and dried to provide 12.51 g, 60.5% yield of colorless crystals. The mother liquor contained 3.72 g (17.9%) of product, for a total yield of 78.2%.

To a suspension of the phthalimide prepared above (12.5 g, 31.8 mmol) in methanol (100 mL) was added anh. hydrazine (5.0 mL, 5.1 g, 159 mmol). The reaction was heated to reflux for 30 min. The volatiles were then removed under vacuum. The residue was dissolved in a mixture of diethyl ether (300 mL), 1 M NaOH (50 mL), and H_2O (200 mL). The layers were separated and the organic layer was washed with 1 M NaOH (50 mL) and the H_2O (3 x 50 mL), dried (anh. Na_2SO_4), and evaporated to give 7.58 g, 95% yield of free base as a colorless oil. This material, dissolved in ethyl acetate (20 mL), was added to a solution of maleic acid 3.5 g, 30.2 mmol in hot ethyl acetate (40 mL). The maleate salt crystallized, was collected, washed with ether (20 mL), and dried under vacuum to provide 9.64 g, 80% (overall yield) colorless crystals. GC/MS t_{R} 6.49 min, m/z 264; TLC 5% MeOH/CHCl₃, rf 0.25.

Synthesis of Compound 219

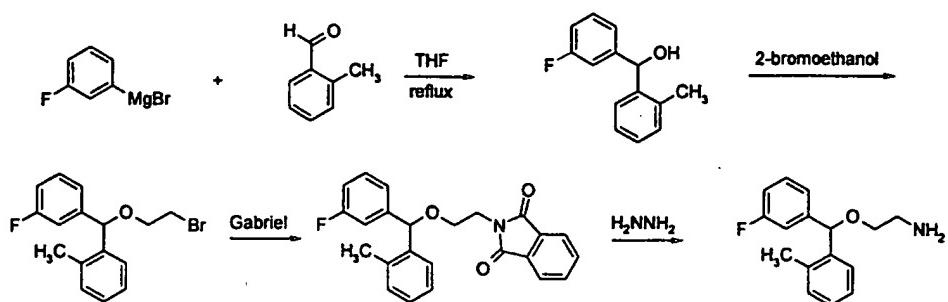


To a solution of 3-fluorobenzophenone (6.67 g, 33.3 mmol) in ethanol (25 mL) was added sodium borohydride (1.40 g, 37.0 mmol). The reaction was exothermic. After stirring 5 min the reaction mixture was rotary evaporated. The 5 resulting material was dissolved in diethyl ether (50 mL), washed with H₂O (2 x 25 mL), dried (anhyd Na₂SO₄), and rotary evaporated. The resultant oil was flash chromatographed (gradient elution: hexane, 9:1 hex/EtOAc, 4:1 hex/EtOAc) through flash silica gel to provide 5.97 g (88.6%) of product.

10 A solution of 3-fluorobenzhydrol (5.97 g, 29.5 mmol), 2-bromoethanol (2.30 mL, 32.4 mmol), and conc. H₂SO₄ (2 drops) in toluene (100 mL) was refluxed for 1 h using a Dean-Stark trap to remove H₂O. The reaction mixture was washed with H₂O (25 mL) and satd. aq. NaCl (25 mL), dried (anhyd. Na₂SO₄), and rotary 15 evaporated (azeotroped with methanol) to provide 7.37 g of crude product. This material was chromatographed (9:1 hex/EtOAc) by MPLC to yield 6.01 g (65.8%) of purified product.

The bromide prepared above (4.90 g, 15.8 mmol) was dissolved in ethanol (100 mL). Concentrated ammonium hydroxide 20 (29% in H₂O; 100 mL) was added. In a 500-mL Parr® apparatus, the reaction mixture was shaken at 90 °C and 65 psig for 4 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (200 mL). The organic layer was dried (anh. Na₂SO₄) and rotary evaporated (azeotroped with benzene) to yield 3.42 g 25 (88.0%) of crude product. This material was dissolved in EtOAc (15 mL) and filtered. The filter was then rinsed with more EtOAc (5 mL). A solution of maleic acid (1.38 g) in EtOAc (20 mL) was added to the combined amine solutions. The acid container was then rinsed with more EtOAc (10 mL). After standing, the 30 resultant crystals were filtered, washed with EtOAc (2 x 20 mL), and dried under high vacuum to provide 3.58 g (62.5%) of maleate salt GC/MS rt 7.12 min, m/z 239; TLC [1:10] MeOH/CHCl₃, rf 0.3.

Synthesis of Compound 220



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Magnesium turnings (1.22 g, 50.2 mmol) were washed with anh. THF (2 x 50 mL). Anh. THF (100 mL) was then added to the magnesium along with a one crystal of iodine and 10% of a solution of 3-bromofluorobenzene (9.61 g, 54.9 mmol) in anh. THF (50 mL). Under argon flow, the reaction mixture was heated to reflux at which time the reaction initiated. The remaining 3-bromofluorobenzene solution was added over a period of 15 min. The reaction mixture was refluxed for 30 min. While still refluxing, o-tolualdehyde (5.48 g, 45.6 mmol) in anh. THF (25 mL) was added over a period of 5 min. The reaction mixture was refluxed for 15 min and was then quenched with satd. aq. NH₄Cl (50 mL). The aqueous layer was separated. The organic layer was washed with satd. aq. NaCl (2 x 50 mL), dried (anh. Na₂SO₄), rotary evaporated (90 °C), and put under high vacuum for 1 h.

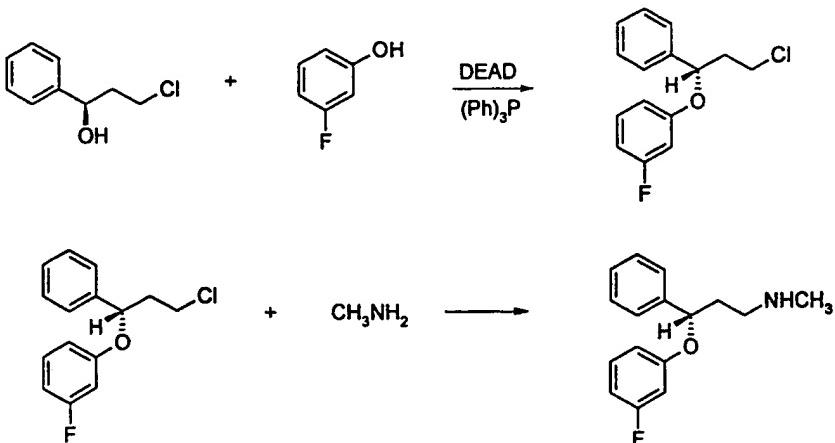
10 This provided 9.06 g (91.9%) of product.

A solution of the substituted benzhydrol prepared above (9.06 g, 41.9 mmol) and 2-bromoethanol (5.76 g, 46.1 mmol) in toluene (100 mL) with H₂SO₄ (2 drops) was refluxed for 1 h using a Dean-Stark trap for 15 min to remove H₂O. The reaction mixture 15 was then rotary evaporated. The residue was dissolved in diethyl ether (100 mL), washed with H₂O (2 x 25 mL), dried (anh. Na₂SO₄), and rotary evaporated to provide 9.71 g (71.7%) of product.

A solution of the above bromide (9.71 g, 30.1 mmol) and potassium phthalimide (5.23 g, 33.1 mmol) in DMF (100 mL) was heated in an oil bath at 120 °C for 60 min. The reaction was then cooled to 25 °C, diethyl ether (400 mL) was added, and the mixture was washed with H₂O (100 mL), 1 M NaOH (100 mL), then H₂O (3 x 100 mL), dried (anh. Na₂SO₄), and then the solvent was evaporated under reduced pressure. The crude material was chromatographed on silica gel (elution with hex/EtOAc [4:1]) to provide 7.96 g, 68.0% of an oil which crystallized on standing.

To a suspension of the above phthalimide (7.96 g, 20.5 mmol) in methanol (100 mL) was added anh. hydrazine (3.2 mL, 3.3 g, 102 mmol). The reaction was heated to reflux for 90 min. The volatiles were then removed under vacuum. The residue was dissolved in a mixture of diethyl ether (300 mL), 1 M NaOH (50 mL), and H₂O (200 mL). The layers were separated and the organic was washed with 1 M NaOH (50 mL) and then H₂O (3 x 50 mL), dried (anh. Na₂SO₄), and evaporated to give 4.47 g, 84.1% yield of an oil.

This material, dissolved in EtOAc (10 mL), was added to a solution of maleic acid (2.00 g, 17.3 mmol) in hot EtOAc (20 mL). The maleate salt crystallized, was collected, washed with diethyl ether (20 mL), and dried under vacuum to provide 5.29 g, 68.8% (overall yield) colorless crystals. GC/MS: m/z = 259, rt = 6.95 min; TLC 5% MeOH/CHCl₃, rf = 0.23.



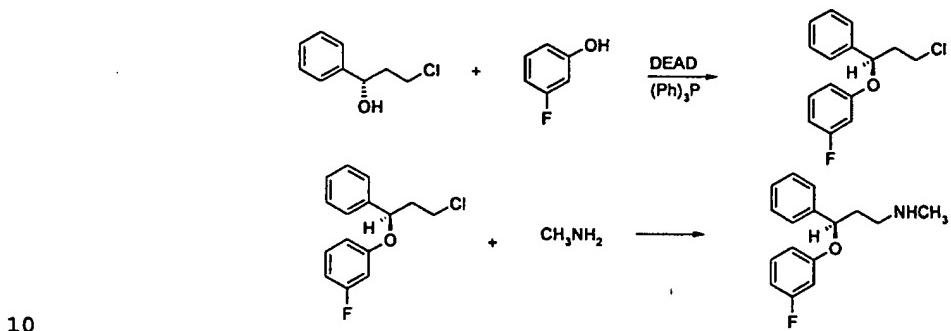
Reference: Mitsunobu, et al., *Synthesis* 1981, 1-28.

In a 500-mL round bottom flask, triphenylphosphine (19.93 g, 5 76.18 mmol) was dissolved in THF (50 mL). To this solution was added (R)-(+)-chloro-1-phenyl-1-propanol (10.00 g, 58.6 mmol) and 3-fluorophenol (6.57 g, 58.6 mmol) and stirred in an ice bath for 10 min. Finally diethyl azodicarboxylate (13.27 g, 76.18 mmol) was added dropwise over 5 min. The reaction was stirred 18 h at 10 25 °C. The reaction was then evaporated under vacuum to yield 19.6 g. The triphenylphosphine oxide was washed and filtered out with diethyl ether (2 x 25 mL), hexane (2 x 25 mL), and pentane (2 x 25 mL) evaporating under vacuum after each wash. The liquid was purified by gravity column, eluted with 40:1 hexane/ethyl 15 acetate (R_f 0.25) to yield 8.90 g. The final purification was by short path distillation; the product was distilled at 140-150 °C under reduced pressure to yield 3.5 g, 26% of a clear oil.

In a Parr flask the chloride, prepared above, (1.65 g, 6.25 mmol) was dissolved in ethanol (80 mL) followed by the addition 20 of methylamine (40% aq., 5.38 mL, 62.5 mmol) and placed in a Parr shaker apparatus for 18 h at 90 °C. At the end of 18 h the solution was evaporated under vacuum. The crude product was the washed 0.1 M NaOH (3 x 25 mL), dried (anh. Na₂SO₄), filtered, and evaporated to 1.4 g. This material was further purified by

column chromatography (10% methanol/CH₂Cl₂) to 0.566 g. The maleate salt was then made by adding a solution of maleic acid (0.234 g, 2.01 mmol) in ethyl acetate (5 mL) to the solution of amine in ethyl acetate (50 mL). To this solution was added 5 hexane (40 mL). The precipitate was then filtered and dried to yield 0.430 g, 26.6% of product as its maleate.

Synthesis of Compound 222



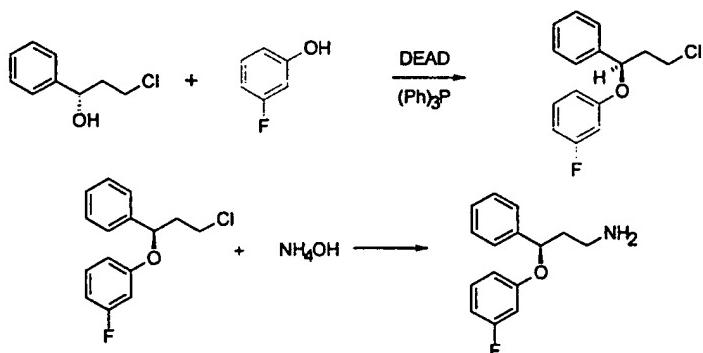
In a 500-mL round bottom flask, triphenylphosphine (19.93 g, 76.18 mmol) was dissolved in THF (50 mL). To this solution was added (S)-(+)-chloro-1-phenyl-1-propanol (10.00 g, 58.6 mmol) 15 and 3-fluorophenol (6.57 g, 58.6 mmol). The reaction was stirred in an ice bath for 10 min. Finally diethyl azodicarboxylate (13.27 g, 76.18 mmol) was added dropwise over 5 min. The reaction was stirred 18 h at 25 °C. The reaction was then evaporated under vacuum to yield 17.5 g. The supernatant was 20 decanted and the triphenylphosphine oxide residue was washed with diethyl ether (2 x 25 mL), hexane (2 x 25 mL), and pentane (2 x 25 mL). The combined washings were evaporated and the residue was purified by gravity column, eluted with 40:1 hexane/ethyl acetate (*R*_f 0.25) to yield 4.5 g, 29% of product.

25 In a Parr flask the chloride prepared above (1.65 g, 6.25 mmol) was dissolved in ethanol (80 mL) followed by the addition of methylamine (40% aq., 5.38 mL, 62.5 mmol) and placed

in a Parr automatic apparatus for 18 h at 90°C. At the end of 18 h the solution was evaporated under vacuum. The residue was then washed with 0.1 M NaOH (3 x 25 mL), dried (anh. Na₂SO₄), filtered, and evaporated to provide 1.25 g. The maleate salt was prepared by adding maleic acid (0.522 g, 4.50 mmol) in ethyl acetate (5 mL) to a solution of amine in ethyl acetate (50 mL). To this solution was added hexane (40 mL) to precipitate the product, which was collected and dried to provide 0.845 g, 52.2% overall.

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Synthesis of Compound 185

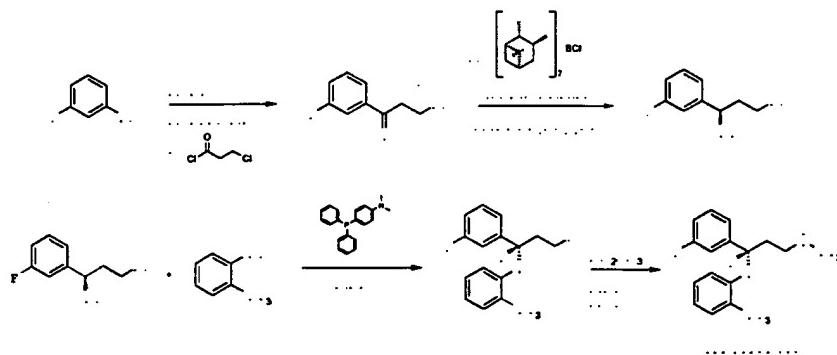


15 In a 500-mL round bottom flask, triphenylphosphine (19.93 g, 76.18 mmol) was dissolved in THF (50 mL). To this solution was added (S)-(+)-chloro-1-phenyl-1-propanol (10.00 g, 58.6 mmol) and 3-fluorophenol (6.57 g, 58.6 mmol). Stirred in an ice bath for 10 min. Finally, diethyl azodicarboxylate (13.27 g, 76.18 mmol) was added dropwise over 5 min. The reaction was stirred 18 h at 25 °C. The reaction was then evaporated under vacuum to yield 17.5 g. The triphenylphosphine oxide was washed and filtered out with ether (2 x 25 mL), hexane (2 x 25 mL), and pentane (2 x 25 mL) evaporating under vacuum after each wash.
20 25 The liquid was purified by gravity column, eluted with 40:1 hexane/ethyl acetate (*R*_f 0.25) to yield 4.5 g, 29% of product.

In a Parr flask the chloride prepared above (1.2 g, 4.54 mmol) was dissolved in ethanol (50 mL). Ammonium hydroxide (40 mL) was added and the reaction mixture was placed in an automatic Parr apparatus for 18 h at 90 °C. At the end of 18 h 5 the solution was evaporated under vacuum. The oil was then transferred to a separatory funnel and washed with 0.1 M NaOH (2 x 25 mL) and water (2 x 25 mL), dried Na_2SO_4 , filtered, and evaporated under vacuum. To a solution of resulting amine (0.703 g) in ethyl acetate (25 mL) was added a solution of maleic acid 10 (0.309 g, 2.66 mmol) in ethyl acetate (5 mL). Hexane (10 mL) was added and the solution stirred until a solid was formed. The resulting white solid was filtered and dried in a vacuum oven to yield 0.600 g of product.

15

Synthesis of Compound 235



Compound 235 was synthesized in a four-step reaction sequence starting from commercially available materials. The Grignard reagent from 3-bromofluorobenzene was reacted with 20 chloropropionyl chloride in the presence of copper bromide and lithium bromide to provide the chlorofluoropropiophenone. Following a method reported in the literature by Srebnik, M., Ramachandran, P.V., and Brown, H.C. (J. Org. Chem., 1988, 53, 2916-2920), the carbonyl group was stereoselectively reduced 25 using (+)-*B*-chlorodiisobutylborane. The resulting enantiomeric alcohol was then converted with stereochemical

inversion to its phenolic ether. The chloride functionality was then reacted with methylamine to provide the final product.

3'-Chloro-3-fluoropropiophenone. The Grignard reagent was prepared as follows. Under nitrogen, in an oven-dried, 2000-mL, 3-necked flask, to a suspension of magnesium turnings [Alpha Aesar, prewashed with diethyl ether (3 x 100 mL), 6.08 g, 250 mmol] in dry diethyl ether (400 mL) was added one crystal of iodine. A solution of 3-bromofluorobenzene (27.9 mL, 250 mmol) in diethyl ether (30 mL) was added dropwise. The reaction mixture was heated to reflux on a hotplate. After initiation, the heat source was removed and the remainder of the bromide was added dropwise over a period of 40 min at such a rate as to maintain steady reflux. The reaction mixture was then heated to reflux for an additional 30 min. The Grignard reaction was then cooled to room temperature with a water bath. The reaction mixture was then cooled in an ice bath and lithium bromide (43.4 g, 500 mmol), copper(I) bromide (35.9 g, 250 mmol), and diethyl ether (300 mL) were added. The ice bath was removed and the dark reaction mixture was allowed to stir at 25 °C for 30 min.

A solution of 3-chloropropionyl chloride (23.9 mL, 250 mmol) in diethyl ether (300 mL) was cooled in an ice bath. The organocuprate solution was then transferred via cannula, over a period of 25 min, to the stirring acid chloride. The dark residue remaining in the flask was washed with diethyl ether (2 x 50 mL) and the washings added to the solution of acid chloride. The ice bath was removed and the reaction mixture was then allowed to stir at 25 °C.

The reaction mixture was then cooled in an ice bath and satd. aq. NH₄Cl (500 mL) was added to the 0 °C reaction mixture with stirring until the color changed from black to green. The mixture was then separated and the aqueous layer was back-extracted with diethyl ether (3 x 150 mL). The combined

organic layers were washed with satd. aq. NH₄Cl (100 mL), dried (anh. Na₂SO₄, Mg₂SO₄), and evaporated under vacuum to provide 34.1 g, 73.0% of an oil. The crude material was dissolved in refluxing hexane (175 mL), filtered through paper, and was 5 chilled 2 h in an ice bath. The resulting low-melting powder was dried to provide 21.3 g, 45.6% of purified ketone.

3-Chloro-3'-fluorophenylpropan-1-ol. Under argon, to a -25 °C (dry ice/acetonitrile/water bath) solution of (+)-DIP-Chloride™ [((+)-B-chlorodiisopinocampheylborane), 16.4 g, 51.0 mmol] in THF (35 mL) was added the ketone (8.65 g, 46.4 mmol). The reaction mixture was then cooled to -25 °C and then allowed to slowly warm to room temperature while stirring for 7 h. The solution was then evaporated under vacuum and dried under high vacuum (0.1 mm, 15 50 °C) for 18 h. The residue was then dissolved in diethyl ether (200 mL). Diethanolamine (13.4 mL 140 mmol) was added and the reaction mixture was stirred for 2 h. The resulting mixture was then filtered and the residue was washed with pentane (3 x 25 mL). The combined filtrate and washings were evaporated in vacuo 20 to provide 16.7 g of an oil which was then placed under high vacuum (0.23 mm, 60 °C) for 18 h to provide 9.51 g. The material was chromatographed on silica gel [elution with hex/EtOAc (10:1)] to provide 5.11 g, 58.4% of an oil.

(S)-1-[3-Chloro-1-(3-fluorophenyl)propoxy]-2-methylbenzene. To a solution of 4-(dimethylamino)phenyldiphenylphosphine (1.98 g, 6.49 mmol) in THF (40 mL) was added 3'-chloro-3-fluorophenylpropanol (1.02 g, 5.41 mmol) followed by ortho-cresol (0.760 g, 7.03 mmol). The reaction mixture was then placed in an 30 ice bath and stirred for 10 min. Diisopropyl azodicarboxylate (DIAD, 1.28 mL 6.49 mmol) was then added dropwise over a period of 1 min. The ice bath was then removed and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture

was then poured into diethyl ether (100 mL) and was washed with 1 M NaOH (2 x 25 mL), 1 M HCl (2 x 25 mL), and brine (25 mL). The organic layer was dried (anh. Na₂SO₄) and evaporated to provide 2.82 g of an oil which crystallized on standing. This material 5 was chromatographed [hex/EtOAc (20:1)] to provide 0.87 g (57.6%) of the product as an oil.

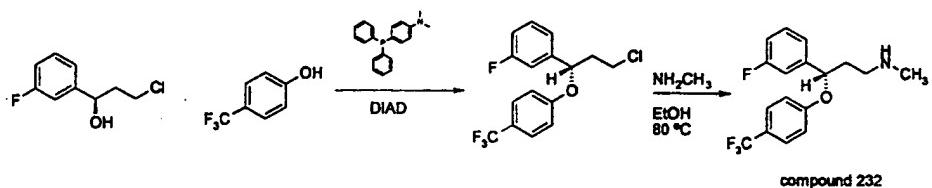
(S)-N-Methyl-3-(3-fluorophenyl)-3-[(2-methylphenyl)oxy]propylamine (Compound 235). In a 500-mL Parr 10 flask (Parr Apparatus), to a solution of the chloro ether (0.435 g, 1.56 mmol) in ethanol (10 mL) was added methylamine (40% aq., 20 mL). The reaction was sealed, heated to 80 °C, and shaken for 24 h. The reaction mixture was then cooled to room temperature and the volatiles were evaporated under vacuum. The resulting 15 oil was dissolved in diethyl ether and the organic layer was washed with satd. aq. NaCl (2 x 10 mL), dried (anh. Na₂SO₄), and rotary evaporated to provide the crude free base as an oil.

This material was purified by reversed-phase HPLC (20-100% acetonitrile in 0.1% aq. HCl gradient) and lyophilized. The 20 amine HCl salt was dissolved in CHCl₃ (50 mL) and "free based" with satd. aq. NaHCO₃ (10 mL). The resulting oil was dissolved in EtOAc (5 mL) and a solution of maleic acid (91 mg) in EtOAc (5 mL) was added. The solution was evaporated to an oil that slowly crystallized to provide 275 mg of the final product.

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Synthesis of Compound 232



Compound 232 was synthesized in a four-step reaction sequence starting from commercially available materials. In a similar pathway as compound 235 was prepared, the Grignard reagent from 3-bromofluorobenzene was reacted with chloropropionyl chloride in the presence of copper bromide and lithium bromide to provide the chlorofluoropropiophenone. Following a method reported in the literature by Srebnik, M., Ramachandran, P.V., and Brown, H.C. (J. Org. Chem. 1988, 53, 2916-2920), the carbonyl group was stereoselectively reduced using (+)-*B*-chlorodiisopropylcamphorborane. The resulting enantiomeric alcohol was then converted with stereochemical inversion to its phenolic ether. The chloride functionality was then reacted with methylamine to provide the final product.

15

(*S*)-1-(3-Chloro-1-(3-fluorophenyl)propoxy)-4-trifluoromethylbenzene. To a solution of 4-(dimethylamino)phenyldiphenylphosphine (1.98 g, 6.49 mmol) in THF (40 mL) was added 3'-chloro-3-fluorophenylpropanol (1.02 g, 5.41 mmol) followed by *para*-trifluoromethylphenol (1.14 g, 7.03 mmol). The reaction mixture was then placed in an ice bath and stirred for 10 min. Then, diisopropyl azodicarboxylate (DIAD, 1.28 mL 6.49 mmol) was added dropwise over a period of 1 min. The ice bath was then removed and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then poured into diethyl ether (100 mL) and washed with 1 M NaOH (2 x 25 mL), 1 M HCl (2 x 25 mL), and brine (25 mL). The organic layer was dried (anh. Na₂SO₄) and evaporated to provide 2.82 g of an oil which crystallized on standing. This material was

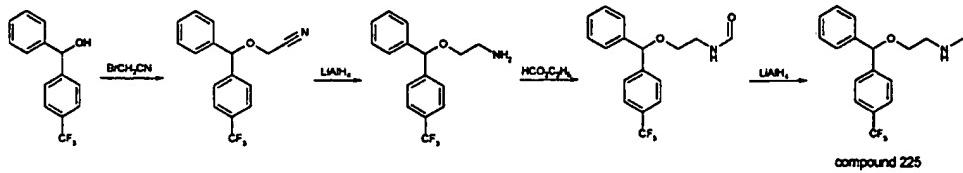
chromatographed (hex/EtOAc [20:1]) to provide 1.06 g (58.8%) of product as an oil.

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(*S*) -*N*-Methyl-3-(3-fluorophenyl)-3-[(4-trifluoromethylphenyl)oxy]propylamine (Compound 232). In a 500-mL Parr flask (Parr Apparatus), to a solution of the chloro ether (0.503 g, 1.51 mmol) in ethanol (10 mL) was added aqueous methylamine (40% aq., 20 mL). The reaction was sealed, was heated to 80 °C (40 psig), and was shaken for 18 h. The reaction mixture was then cooled to room temperature and the volatiles were evaporated under vacuum. The resulting oil was dissolved in diethyl ether (100 mL), the organic layer washed with satd. aq. NaCl (2 x 10 mL), dried (anh. Na₂SO₄), and rotary evaporated to provide the crude free base as an oil. This material was chromatographed on silica gel (0-10% MeOH/CHCl₃, gradient elution) to provide 450 mg of product as an oil.

This material was further purified by reversed-phase HPLC (20%-100% acetonitrile in 0.1% aq. HCl, gradient) and lyophilized. The amine HCl salt was dissolved in CHCl₃ (50 mL) and free based with satd. aq. NaHCO₃ (10 mL). The resulting oil (230 mg) was dissolved in EtOAc (5 mL) and a solution of maleic acid (81 mg) in EtOAc (5 mL) was added. The solution was evaporated under high vacuum to an oil that slowly crystallized to provide 150 mg of final product.

Synthesis of Compound 225



Compound 225 was synthesized in four steps from commercially available starting materials. 4-
Trifluoromethylbenzhydrol was reacted with bromoacetonitrile under basic phase-transfer conditions to synthesize the
5 benzhydrylacetonitrile ether. The nitrile was then reduced to the primary amine. The amine was N-methylated in two steps by reduction of its corresponding formamide.

[1-Phenyl-1-(*p*-trifluoromethylphenyl)methoxy]acetonitrile. A mixture of 4-trifluoromethylbenzhydrol (24.36 g, 97 mmol),
10 tetrabutylammonium hydrogen sulfate (0.45 g, 1.3 mmol), CH₂Cl₂ (40 mL), and 50% aq. NaOH (10.53 g NaOH, 263 mmol) was stirred at 20 °C for 1 h. The reaction mixture was then cooled to 0 °C and bromoacetonitrile (12.5 mL, 179 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. The reaction
15 mixture was diluted with diethyl ether (200 mL) and washed with water until the washings were neutral (10 x 50 mL). The organic layer was dried (anh. MgSO₄), filtered, and rotary evaporated (33.73 g, 120%). This material was chromatographed (CHCl₃) through silica gel to yield 21.0 g (75%) of the product as an
20 oil.

[1-Phenyl-1-(*p*-trifluoromethylphenyl)methoxyethylamine. To lithium aluminum hydride (1.10 g, 29.0 mmol) was added anh. diethyl ether (100 mL). This mixture was stirred under argon flow for 5 min. The nitrile prepared above (5.00 g, 17.2 mmol)
25 in anh. diethyl ether (5 mL) was added over a period of 2 min (rinsing the nitrile container with 5 mL diethyl ether). The reaction was stirred for 30 min [TLC (4:1 hex/EtOAc) showed no starting material after 15 min]. To the reaction mixture was slowly added ethyl acetate (5 mL), followed by water (1.1 mL),
30 5 M NaOH (1.1 mL), and then more water (3.3 mL). The reaction mixture was filtered through paper, and the filtrate was dried (anh. Na₂SO₄) and rotary evaporated (75 °C) to provide 4.25 g (83.8%) of the product as an oil. This oil was flash

chromatographed (CHCl₃, 1:20 MeOH/CHCl₃, step gradient) through flash silica gel to provide 3.52 g (69.4%) of the product as an oil.

[1-Phenyl-1-(*p*-trifluoromethylphenyl)methoxy]ethylamine
5 formamide. The primary amine prepared above (2.13 g, 7.21 mmol) was dissolved in ethyl formate (40 mL, 500 mmol). The reaction solution was refluxed for 15 h, and was then rotary evaporated. This provided 2.42 g (104%) of the product as an oil. This oil was flash chromatographed (hexanes, 1:1 hex/EtOAc,
10 EtOAc, step gradient) through flash silica gel to provide 1.71 g (73.3%) of the product as an oil.

N-Methyl-[1-phenyl-1-(*p*-trifluoromethylphenyl)methoxy]ethylamine.
To lithium aluminum hydride (0.30 g, 7.9 mmol) was added anh. diethyl ether (20 mL). This mixture was stirred under argon flow
15 for 5 min. The formamide prepared above (1.68 g, 5.20 mmol) in anh. diethyl ether (5 mL) was added over a period of 1 min (rinsing the nitrile container with 5 mL diethyl ether). The reaction was stirred for 20.5 h [TLC (EtOAc) showed almost no starting material after 4.5 h]. To the reaction mixture was
20 slowly added EtOAc (0.3 mL), followed by water (0.3 mL), 5 M NaOH (0.3 mL), and then more water (0.9 mL). The reaction mixture was filtered through paper, and the filtrate was dried (anh. Na₂SO₄) and rotary evaporated (75 °C) to provide 1.43 g (89.0%) of the product as an oil. This oil was flash chromatographed (EtOAc,
25 1:20 MeOH/CHCl₃, 1:1 MeOH/CHCl₃, step gradient) through flash silica gel to provide 0.91 g (57%) of the product as an oil. This material was dissolved in EtOAc (2 mL) and filtered. To the filtrate was added a solution of maleic acid (0.31 g, 2.7 mmol) in EtOAc (5 mL). To this solution was added diethyl ether
30 (15 mL). Crystals formed, were filtered, washed with diethyl ether (2 x 10 mL), and dried under high vacuum to provide 888 mg (40.2%) of the maleate salt as a finely crystalline solid.

Other embodiments are within the following claims. Thus, while several embodiments have been shown and described, various modifications may be made without departing from the spirit and scope of the present invention.

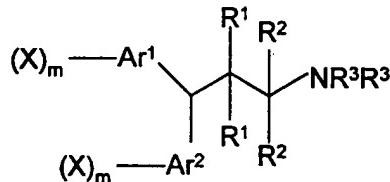
Claims

1. A method of treating a patient for depression comprising the step of administering to said patient an effective amount of a compound having a NMDA IC₅₀ of about 50 nM to about 1 μM as measured in the NMDA assay and a serotonin reuptake IC₅₀ of less than or equal to about 100 nm as measured in the serotonin reuptake inhibition assay.

10 2. The method of claim 1, wherein said compound has an NMDA receptor IC₅₀ of 50 nM to 1 μM and a SSRI IC₅₀ less than 100 nM.

15 3. A method of treating a patient for depression comprising the step of administering to said patient an effect amount of a compound having the chemical structure:

15



wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, and -O-acyl;

20 Ar¹ and Ar² are each independently selected from the group consisting of phenyl, naphthyl, thiofuranyl, tetrahydronaphthyl, furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl, cycloheptyl, and cyclopentyl;

25 each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;

each R² is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino;

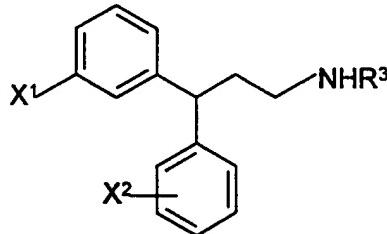
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each R³ is independently selected from the group consisting of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; and
 each m is independently an integer from 0 to 5;
 provided that if both R₃'s are -CH₃, then both X_m's are not
 5 3-F, 4-F, 3-CF₃, 4-Cl, and if both R₃'s are -CH₃, and one X_m is 4-F
 then the other X_m is not 4-Cl; further provided that if one R₃ is
 -H and the other R₃ is -CH₃, then both X_m's are not 4-Cl, and if
 one R₃ is -H and the other R₃ is -CH₃, then at least one m is 1;
 or a pharmaceutically acceptable salt thereof.

10

4. The method of claim 3 wherein for said compound each X is independently either -F, -Cl, -OCF₃ or -CF₃;
 each R¹ is -H;
 each R² is -H;
 15 one R³ is -H, and the other R³ is either -H or -CH₃; and
 each m is 1.

5. The method of claim 3 wherein said compound has the chemical structure:



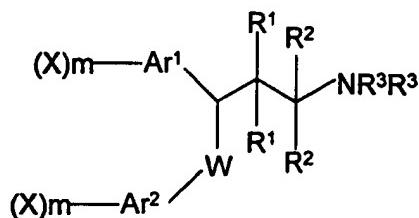
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wherein X¹ is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl;
 X² is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃,
 25 -O-alkyl, or -O-acyl; and
 R³ is either -H or -CH₃;
 or a pharmaceutically acceptable salt thereof.

6. The method of claim 5, wherein X¹ is -F, -Cl, -OCF₃ or -CF₃; and X² is either 2-OCH₃, 2-CH₃, 3-F, 3-CF₃, or 4-CF₃.

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7. A method of treating a patient for depression comprising the step of administering to said patient an effective amount of a compound having the chemical structure:



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wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, and -O-acyl;

Ar¹ and Ar² are each independently selected from the group consisting of phenyl, naphthyl, thifuranyl, tetrahydronaphthyl, furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl, cycloheptyl, and cyclopentyl;

each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;

each R² is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino;

each R³ is independently selected from the group consisting of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; and

20 m is 0 to 5;

or a pharmaceutically acceptable salt thereof.

8. The method of claim 7, wherein for said compound each X is independently either -F, -Cl, -OCF₃, or -CF₃;

25 Ar¹ and Ar² are each independently phenyl or naphthyl;

each R¹ is -H;

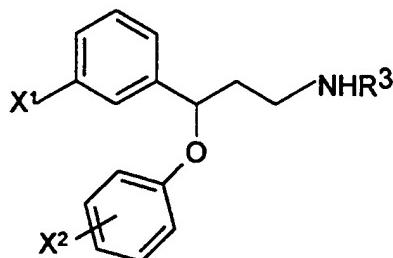
each R² is -H;

one R³ is -H, and the other R³ is either -H or -CH;

each m is 0 or 1.

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9. The method of claim 7, wherein said compound has the chemical structure:



5 wherein X^1 is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl;

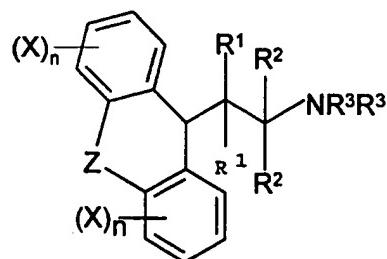
X^2 is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl; and

 R³ is either -H or -CH₃;

10 or a pharmaceutically acceptable salt thereof.

10. The method of claim 9 wherein X^1 is either -F, -Cl, -OCF₃ or -CF₃; and X^2 is either 2-OCH₃, 2-CH₃, 3-F, 3-CF₃, or 4-CF₃.

15 11. A method of treating a patient for depression comprising the step of administering to said patient an effective amount of a compound having the chemical structure:



20 wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, and -O-acyl;

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each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl;

each R² is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino;

5 each R³ is independently selected from the group consisting of -H, alkyl, 2-hydroxyethyl, and alkylphenyl;

Z is either -CH₂CH₂-, -CH₂CH(CH₃)-, -CH=CH-, -O-CH₂-, -S-CH₂-, -CH₂-, -O-, or -S-; and

each n is independently 1 to 4; or a pharmaceutically acceptable salt thereof.

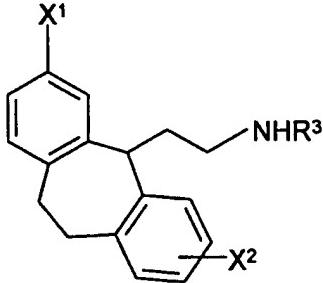
12. The compound of claim 11, wherein each X is independently either -F, -Cl, -OCF₃ or -CF₃;

each R¹ is -H;

each R² is -H;

15 one R³ is -H, and the other R³ is either -H or -CH; and each n is 1.

13. The method of claim 11, wherein said compound has the chemical structure:



20

wherein X¹ is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl;

X² is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, or -O-acyl; and

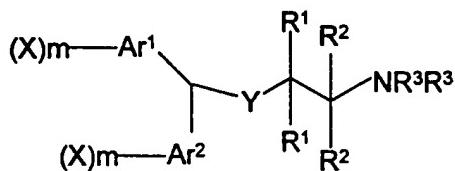
25 R³ is either -H or -CH₃;

or a pharmaceutically acceptable salt thereof.

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14. The method of claim 13 wherein X^1 is -F, -Cl, -OCF₃, or -CF₃; and X^2 is either either -F, -Cl, -OCH₃, -CH₃, -OCF₃, or -CF₃.

5 15. A method of treating a patient for depression comprising the step of administering to said patient an effect amount of a compound having the chemical structure:



10 wherein each X is independently selected from the group consisting of -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃, -O-alkyl, and -O-acyl; preferably, each X is independently either -F, -Cl, -OCF₃, or -CF₃;

15 Ar¹ and Ar² are each independently selected from the group consisting of phenyl, naphthyl, thiofuranyl, tetrahydronaphthyl, furanyl, tetrahydrofuranyl, pyridyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, cyclohexyl, cycloheptyl, and cyclopentyl; preferably Ar¹ and Ar² are independently naphthyl or phenyl; more preferably at least one of 20 Ar¹ and Ar² is phenyl; and more preferably, both Ar¹ and Ar² are phenyl;

Y is either -CH₂- , -O- , or -S- ;

each R¹ is independently selected from the group consisting of -H, alkyl, hydroxyalkyl, -OH, -O-alkyl, and -O-acyl; 25 preferably, each R¹ is -H;

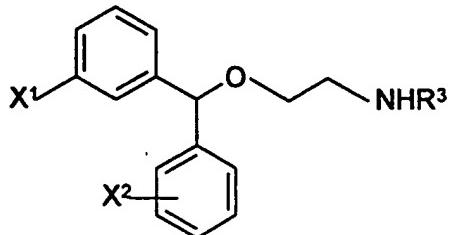
each R² is independently selected from the group consisting of -H, alkyl, and hydroxyalkyl, or both R²'s together are imino; preferably each R² is -H;

each R³ is independently selected from the group consisting 30 of -H, alkyl, 2-hydroxyethyl, and alkylphenyl; preferably, each R³ is independently either -H or -CH₃; more preferably one R³ is -H, and the other R³ is either -H or -CH₃; and

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each m is independently an integer from 0 to 5; and
 preferably, each m is independently 0 or 1.

16. The method of claim 15, wherein said compound has the
 5 chemical structure; Structure VIII



wherein X¹ is independently selected from the group
 consisting of -H, -Br, -Cl, -F, -I, -CF₃, alkyl, -OH,
 10 -OCF₃, -O-alkyl, or -O-acyl; preferably, X¹ is either -F, -Cl,
 -OCF₃, and -CF₃;
 X² is either -Br, -Cl, -F, -I, -CF₃, alkyl, -OH, -OCF₃,
 -O-alkyl, or -O-acyl; preferably, X² is independently either -F,
 -Cl, -OCH₃, -CH₃, -OCF₃ or -CF₃; more preferably, X² is either 2-
 15 OCH₃, 2-CH₃, 3-F, 3-CF₃, or 4-CF₃; and
 R³ is either -H or CH₃;
 or a pharmaceutically acceptable salt thereof.

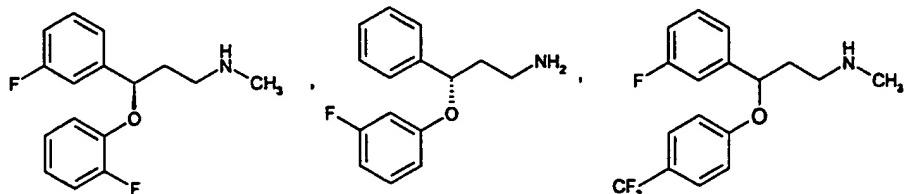
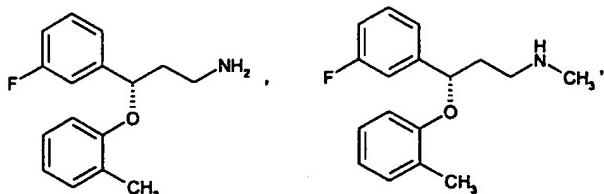
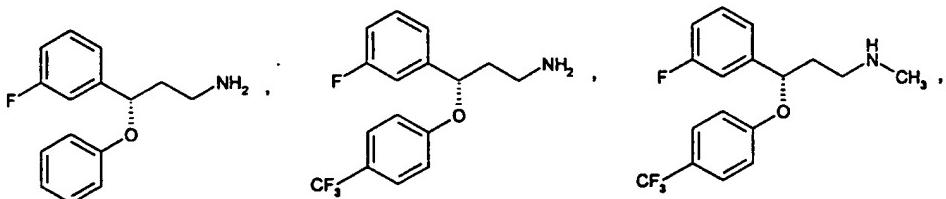
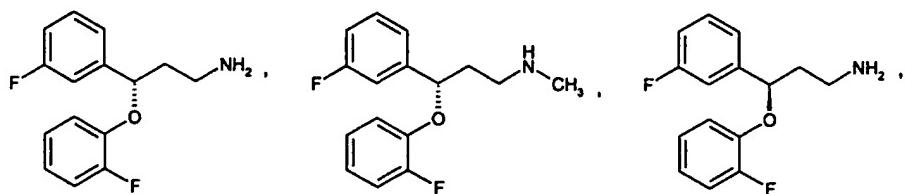
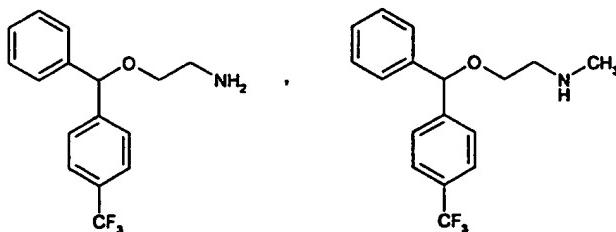
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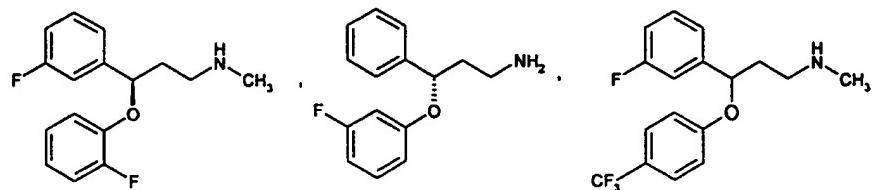
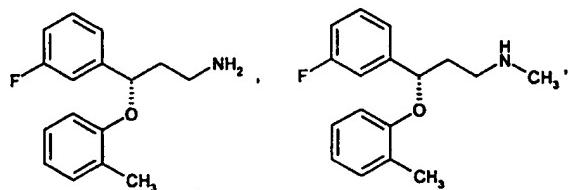
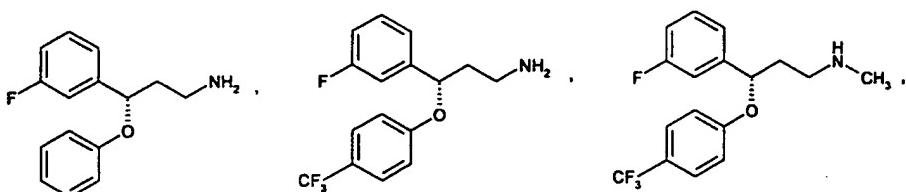
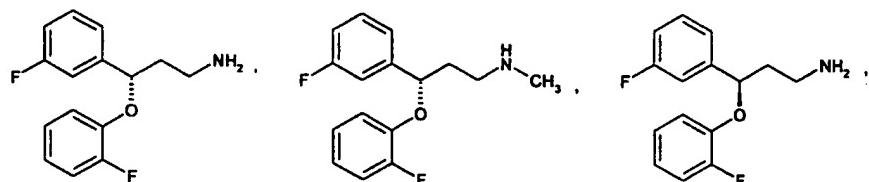
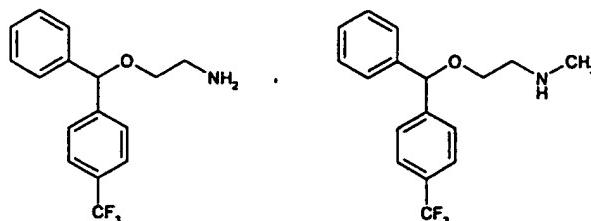
17. A compound having the chemical structure;



or a pharmaceutically acceptable salt thereof.

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18. A method of treating a patient for depression comprising the step of administering to said patient an effect amount of a compound having the chemical structure:



5 or a pharmaceutically acceptable salt thereof.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 31/135, 31/137, 31/138, 31/4462, 31/00, 31/352, 31/382, 31/335, C07C 217/00		A3	(11) International Publication Number: WO 00/02551 (43) International Publication Date: 20 January 2000 (20.01.00)
(21) International Application Number: PCT/US99/15857		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 12 July 1999 (12.07.99)			
(30) Priority Data: 60/092,546 13 July 1998 (13.07.98) US			
(71) Applicant (<i>for all designated States except US</i>): NPS PHARMACEUTICALS, INC. [US/US]; Suite 240, 420 Chipeta Way, Salt Lake City, UT 84018-1256 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (<i>for US only</i>): MUELLER, Alan [US/US]; 2510 East Skyline Drive, Salt Lake City, UT 84108 (US). MOE, Scott [US/US]; 1979 E. Forest Creek Lane, Salt Lake City, UT 84121 (US). BALANDRIN, Manuel [US/US]; 9184 South Winter Wren Drive, Sandy, UT 84093 (US).			
(74) Agent: WARBURG, Richard, J.; Lyon & Lyon LLP, Suite 4700, 633 West Fifth Street, Los Angeles, CA 90071-2066 (US).			

(54) Title: METHODS AND COMPOUNDS FOR TREATING DEPRESSION

(57) Abstract

The present invention features compounds active at both the serotonin uptake site and the N-methyl-D-aspartate (NMDA) receptor and the use of such compounds for treating different disorders. Compounds having activity at the serotonin reuptake site and the NMDA receptor ("multi-active compounds") can be used to treat different types of disorders such as depression, obsessive-compulsive disorders (OCD), sleep disorders, sexual dysfunction, and eating disorders. Preferably, the multi-active compounds are used to treat depression.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/15857

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	A61K31/135	A61K31/137	A61K31/138	A61K31/4462	A61K31/00
	A61K31/352	A61K31/382	A61K31/335	C07C217/00	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILKINSON A ET AL: "Alaproclate acts as a potent, reversible and noncompetitive antagonist of the NMDA receptor coupled ion flow." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 DEC) 271 (3) 1314-9., XP000862851 the whole document ---	1,2
X	EP 0 000 322 A (ASTRA LAEKEMEDEL AB) 10 January 1979 (1979-01-10) the whole document ---	1-3
X	FR 2 077 916 A (DAINIPPON PHARMACEUTICAL CO) 5 November 1971 (1971-11-05) the whole document ---	1-3

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

Date of mailing of the international search report

21 January 2000

19.06.00

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INTERNATIONAL SEARCH REPORT

Internati	Application No
	PCT/US 99/15857

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARYANOFF ET AL: "Structure-Activity Studies on Antidepressant 2,2-Diarylethylamines" JOURNAL OF MEDICINAL CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY, WASHINGTON, vol. 27, page 1067-1071 XP002083434 ISSN: 0022-2623 Table I, compounds 34,35,37 page 1067, right-hand column, last paragraph ---	1-3
X	CARNMALM, BERNST ET AL: "Antidepressant agents. V. 1,1-Dimethyl-.omega.,.omega.-diphenylalkylamines" ACTA PHARM. SUEC. (1975), 12(2), 173-82, XP000862860 the whole document ---	1-3
X	MARCUSSON J O ET AL: "INHIBITION OF U3HPAROXETINE BINDING BY VARIOUS SEROTONIN UPTAKE INHIBITORS: STRUCTURE-ACTIVITY RELATIONSHIPS" EUROPEAN JOURNAL OF PHARMACOLOGY, NL, AMSTERDAM, vol. 215, no. 2/03, page 191-198 XP002016630 ISSN: 0014-2999 abstract table 4 ---	1-3
X	WO 96 40097 A (NPS PHARMA INC) 19 December 1996 (1996-12-19) abstract page 1, line 18 -page 2, line 11 page 60, line 22 -page 69 page 224 last compound claims 1-5,8-13,18-33 ---	1-3
Y	WO 97 46511 A (VANWAGENEN BRADFORD C; DELMAR ERIC G (US); MOE SCOTT T (US); SMITH) 11 December 1997 (1997-12-11) abstract page 1, line 20 -page 2, line 12 page 61, line 19 -page 74 page 236 "astral compound" claims 1-27 ---	4-6
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Y	NOWAK G ET AL: "Adaptation of cortical NMDA receptors by chronic treatment with specific serotonin reuptake inhibitors." EUROPEAN JOURNAL OF PHARMACOLOGY, (1998 JAN 26) 342 (2-3) 367-70., XP000862854 the whole document ---	4-6
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INTERNATIONAL SEARCH REPORT

Internati	Application No
PCT/US 99/15857	

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>PAUL I A ET AL: "ADAPTATION OF THE N-METHYL-D-ASPARTATE RECEPTOR COMPLEX FOLLOWING CHRONIC ANTIDEPRESSANT TREATMENTS" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, US, AMERICAN SOCIETY FOR PHARMACOLOGY AND, vol. 269, no. 1, page 95-102 XP002016627 ISSN: 0022-3565 the whole document</p> <p>---</p>	4-6
A	<p>WO 95 21612 A (NPS PHARMA INC.; MUELLER ALAN L (US); WAGENEN BRADFORD C VAN (US);) 17 August 1995 (1995-08-17)</p> <p>abstract</p> <p>page 1, line 1 - line 19 page 31, line 6 -page 37, line 5; claims 14-19</p> <p>-----</p>	1-6

INTERNATIONAL SEARCH REPORTInt'l application No.
PCT/US 99/15857**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
· Although claims 1-6 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 1-2 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see FURTHER INFORMATION PCT/ISA/210

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2 partially, 3-6

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-2 (partially),3-6

Method of treating depression with a compound of structure I, such as defined in claim 3

2. Claims: 1-2(partially),7-10,17-18(partially)

Method of treating depression with a compound of structure II, such as defined in claim 7

3. Claims: 1-2(partially),11-14

Method of treating depression with a compound of structure III, such as defined in claim 11

4. Claims: 1-2(partially), 15-16,17-18(partially)

Method of treating depression with a compound of structure VII, such as defined in claim 15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-2

Present claims 1-2 relate to a compound defined by reference to a desirable characteristic or property, namely "having NMDA IC₅₀ of " and "serotonin reuptake IC₅₀ of".

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search for the subject-matters of claims 1-2 is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by its pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search for the subject-matters of claims 1-2 impossible.

Furthermore, present claims 3-4 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds mentioned in claims 5,6 and to the general idea underlying the present invention .

Claims searched completely: 5,6

Claims searched incompletely: 3-4

Claims not searched: 1-2

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Info. on patent family members

International Application No
PCT/US 99/15857

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0000322 A	10-01-1979	GB 1602290 A DE 2861781 D EP 0028682 A IE 47628 B IT 1162317 B JP 55011563 A AT 363456 B AT 483578 A AT 368988 B AT 493380 A AU 519960 B AU 3761278 A CA 1111041 A DK 295178 A FI 782093 A,B, IT 1105075 B JP 54039057 A NO 782305 A,B,		11-11-1981 24-06-1982 20-05-1981 16-05-1984 25-03-1987 26-01-1980 10-08-1981 15-01-1981 25-11-1982 15-04-1982 07-01-1982 03-01-1980 20-10-1981 05-01-1979 05-01-1979 28-10-1985 24-03-1979 05-01-1979
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